STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 17342

TO: Kevin Weddington Location: REM-3A65/3C70 Art Unit: 1614 Friday, December 09, 2005 Case Serial Number: 10/712296	From: Mary Hale Location: Biotech/Chem Library Rem 1D86 Phone: 2-2507 Mary.Hale@uspto.gov

Search Notes

Feel free to contact me if you have any questions.

Note -- results are printed on both sides of printout

KEM · ~~SA~~ SC70

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: K. Weddington Examiner #: 68082 Date: 12-1-05
Art Unit: 1614 Phone Number: 2-0587 Serial Number: 10/712,296
Location (Bldg/Room#):_____ (Mailbox #):_____ Results Format Preferred (circle): PAPER DISK
****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: _____

Inventors (please provide full names): Tinya Abrams; Lesley Murray; Nancy Dyer

Earliest Priority Date: _____

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only ***Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.***

Treating cancer with a composition comprising

1) An indolinone of formula I

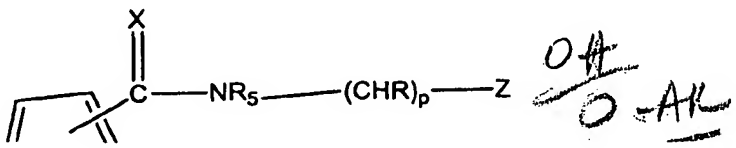
2) a chemotherapeutic agent such as pharmacothera drug therap

carboplatin, cisplatin, doxorubicin, irinotecan, docetaxel, paclitaxel, 5-fluorouracil or leucovorin

RECEIVED
DEC - 2 2005
GROUP 1614

What is claimed is:

1. A method of treating cancer comprising administering to a patient in need thereof an effective amount of a compound of Formula I:



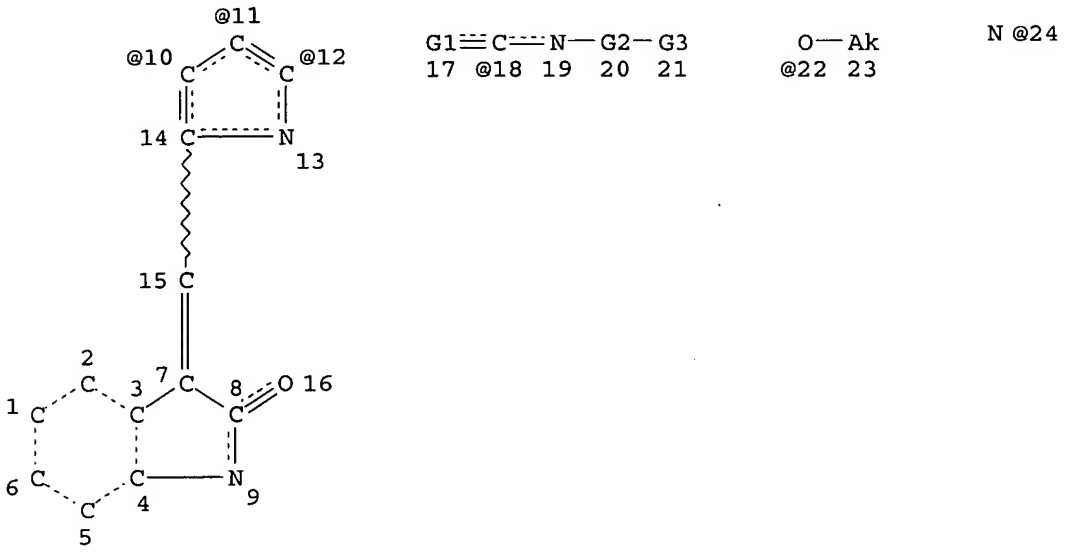
Weddington
10/712296

=> dis his

(FILE 'HOME' ENTERED AT 15:17:16 ON 09 DEC 2005)

FILE 'REGISTRY' ENTERED AT 15:17:24 ON 09 DEC 2005
L1 STR
L2 26 S L1
L3 STR L1
L4 642 S L3 FUL

=> d l4 que stat;fil medl,biosis,embase,caplus;s l4
L3 STR



VAR G1=O/S
REP G2=(0-3) CH
VAR G3=OH/22/24
VPA 18-12/11/10 U
NODE ATTRIBUTES:
NSPEC IS RC AT 24
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE
L4 642 SEA FILE=REGISTRY SSS FUL L3

100.0% PROCESSED 2849 ITERATIONS 642 ANSWERS
SEARCH TIME: 00.00.01

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	164.34	164.55

FILE 'MEDLINE' ENTERED AT 15:22:21 ON 09 DEC 2005

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

FILE 'BIOSIS' ENTERED AT 15:22:21 ON 09 DEC 2005

FILE 'EMBASE' ENTERED AT 15:22:21 ON 09 DEC 2005

FILE 'CAPLUS' ENTERED AT 15:22:21 ON 09 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

L5 0 FILE MEDLINE
L6 49 FILE BIOSIS
L7 262 FILE EMBASE
L8 94 FILE CAPLUS

TOTAL FOR ALL FILES
L9 405 L4

=> s chemotherap? or pharmacotherap?
L10 193240 FILE MEDLINE
L11 141918 FILE BIOSIS
L12 223085 FILE EMBASE
L13 74470 FILE CAPLUS

TOTAL FOR ALL FILES
L14 632713 CHEMOTHERAP? OR PHARMACOTHERAP?

=> fil reg;s (carboplatin or cisplatin or doxorubicin or irinotecan or docetaxel or paclitaxel or "5-fluorouracil" or leucovorin)/cn
COST IN U.S. DOLLARS SINCE FILE ENTRY 45.30 TOTAL SESSION 209.85
FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 15:24:09 ON 09 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 8 DEC 2005 HIGHEST RN 869627-02-1
DICTIONARY FILE UPDATES: 8 DEC 2005 HIGHEST RN 869627-02-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *

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*                                                                    *
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Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html


             1 CARBOPLATIN/CN
             1 CISPLATIN/CN
             1 DOXORUBICIN/CN
             1 IRINOTECAN/CN
             1 DOCETAXEL/CN
             1 PACLITAXEL/CN
             1 "5-FLUOROURACIL"/CN
             1 LEUCOVORIN/CN
L15          8 (CARBOPLATIN OR CISPLATIN OR DOXORUBICIN OR IRINOTECAN OR DOCETA
               XEL OR PACLITAXEL OR "5-FLUOROURACIL" OR LEUCOVORIN)/CN

=> fil medl,biosis,embase,caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               37.23     247.08

FILE 'MEDLINE' ENTERED AT 15:24:26 ON 09 DEC 2005

FILE 'BIOSIS' ENTERED AT 15:24:26 ON 09 DEC 2005
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FILE 'EMBASE' ENTERED AT 15:24:26 ON 09 DEC 2005
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FILE 'CAPLUS' ENTERED AT 15:24:26 ON 09 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

=> s carboplatin or cisplatin or doxorubicin or irinotecan or docetaxel or
paclitaxel or "5-fluorouracil" or leucovorin or l15
L16       92658 FILE MEDLINE
L17       98308 FILE BIOSIS
L18      159143 FILE EMBASE
L19       63676 FILE CAPLUS

TOTAL FOR ALL FILES
L20      413785 CARBOPLATIN OR CISPLATIN OR DOXORUBICIN OR IRINOTECAN OR DOCETAX
                EL OR PACLITAXEL OR "5-FLUOROURACIL" OR LEUCOVORIN OR L15

=> s l9 and l14 and l20
L21           0 FILE MEDLINE
L22           2 FILE BIOSIS
L23          61 FILE EMBASE
L24          13 FILE CAPLUS


Prepared by: Mary Hale @2-2507 Rem Bldg 1D86
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TOTAL FOR ALL FILES
L25 76 L9 AND L14 AND L20

=> dup rem l25
PROCESSING COMPLETED FOR L25
L26 73 DUP REM L25 (3 DUPLICATES REMOVED)

=> d 1-73 ibib abs fhitstr;s abrams t?/au;s murray l?/au;s pryer n?/au or dryer n?/au

L26 ANSWER 1 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:984120 CAPLUS
DOCUMENT NUMBER: 143:279360
TITLE: Methods of detecting CD133 antigen (AC133) expression level and use as biomarker for human cancer diagnosis and therapy monitor
INVENTOR(S): Penning, Maarten Tjerk; Van den Broek, Sebastiaan Johannes Jacobus; Voest, Emile Eugene; Beerepoot, Laurens Victor; Mehra, Niven
PATENT ASSIGNEE(S): Primagen Holding B. V., Neth.; UMC Utrecht Holding B. V.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

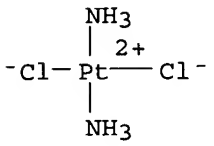
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005083123	A1	20050909	WO 2005-NL155	20050302
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1571225	A1	20050907	EP 2004-75686	20040302
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				

PRIORITY APPLN. INFO.:
EP 2004-75686 A 20040302
US 2004-549450P P 20040302

AB This invention provides methods of detecting CD133 antigen (AC133) expression level and use as a biomarker for human cancer diagnosis and therapy monitor. Blood anal. including number of circulating endothelial cells and expression levels of human genes AC133 (CD133), EST032 and U1A evaluated by NASBA anal., were determined prior to and during **chemotherapy** using drugs such as angiostatin or PrimMed01, gemcitabine, and **cisplatin**, for a wide range of human tumor types. A use of a nucleic acid mol. comprising at least part of a sequence of AC133 or an analog thereof for monitoring a treatment of an individual suffering from a disease is also provided, as well as a diagnostic kit comprising such nucleic acid mol.

IT **15663-27-1, Cisplatin**
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(methods of detecting CD133 antigen (AC133) expression level and use as biomarker for human cancer diagnosis and therapy monitor)
RN 15663-27-1 CAPLUS
CN Platinum, diamminedichloro-, (SP-4-2)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 2 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:962021 CAPLUS
DOCUMENT NUMBER: 143:272421
TITLE: Combination composition comprising an antagonist of tissue factor (TF) and an anticancer compound for treating disorders related to TF dysfunction
INVENTOR(S): Mueller, Jorn Roland
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005079766	A2	20050901	WO 2005-DK98	20050214
WO 2005079766	A3	20051013		

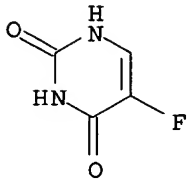
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DK 2004-264 A 20040220
AB The present invention relates to a novel pharmaceutical compns. comprising a combination of a compound, which binds to and inhibits the activity of tissue factor (TF) and a anti-cancer **chemotherapeutic** compound The invention also relates to their use in the prophylaxis or treatment of diseases or disorders related to TF dysfunction, including cancers, inflammation, atherosclerosis and ischemia. The TF antagonists bind TF with high affinity and specificity but do not initiate blood coagulation. In one embodiment of the present invention the TF antagonist is factor VIIa (FVIIa) polypeptides chemical inactivated in the active site with chloromethyl ketone inhibitor. In another embodiment of the present invention the TF antagonist is an antibody against TF, particularly fully human antibody. In one embodiment of the present invention the TF

antagonist is a fully human antibody against TF, particularly antibody binding with an TF epitope. In a further embodiment of the invention the isolated human antibody binds to an TF epitope within the interface between TF and FVIa.

IT **51-21-8, 5-Fluorouracil**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination composition comprising antagonist of tissue factor (TF) and anticancer compound for treating disorders related to TF dysfunction)

RN 51-21-8 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI) (CA INDEX NAME)



L26 ANSWER 3 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:588556 CAPLUS
DOCUMENT NUMBER: 143:115395
TITLE: Preparation of derivatives of gambogic acid and analogs as activators of caspases and inducers of apoptosis
INVENTOR(S): Cai, Sui Xiong; Jiang, Songchun; Zhang, Han-Zhong
PATENT ASSIGNEE(S): Cytovia, Inc., USA
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005060663	A2	20050707	WO 2004-US42292	20041217

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-530256P P 20031218
GI

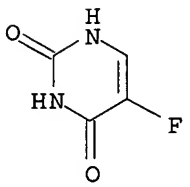
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention is directed to novel derivs. of gambogic acid (I)

and analogs thereof. Thus, 2-(Dimethylamino)ethyl gambogate (II) was prepared from I via esterification with ClCH2CH2NMe2·HCl in the presence of KI and Cs2CO4. The present invention also relates to the discovery that novel derivs. of gambogic acid are activators of caspases and inducers of apoptosis. Therefore, the activators of caspases and inducers of apoptosis of this invention can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs. The bioactivity of II was determined [caspase cascade activation EC50 = 676 nM vs. T-47D and EC50 = 1041 nM vs. DLD breast cancer cells; cell proliferation inhibition GI50 = 187 nM (vs. T-47D), GI50 = 173 nM (vs. DLD), GI50 = 101 nM (vs. MX-1), GI50 = 180 nM (vs. SW620), GI50 = 184 nM (vs. H1299), GI50 = 440 nM (vs. HEK293T), GI50 = 192 nM (vs. HEK293H)].

IT **51-21-8, 5-Fluorouracil**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination **chemotherapy** co-agent; preparation of derivs. of gambogic acid and analogs as activators of caspases and inducers of apoptosis)

RN 51-21-8 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI) (CA INDEX NAME)



L26 ANSWER 4 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:371491 CAPLUS
DOCUMENT NUMBER: 142:423817
TITLE: Anti-vascular and anti-proliferation methods, therapies, and combinations employing specific tyrosine kinase inhibitors
INVENTOR(S): Nesbit, Mark; Spada, Alfred P.; He, Wei; Myers, Michael R.
PATENT ASSIGNEE(S): Gencell Sas, Fr.; Aventis Pharmaceuticals Inc.
SOURCE: PCT Int. Appl., 156 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005038465	A2	20050428	WO 2004-EP12185	20041007
WO 2005038465	A3	20050915		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-508859P P 20031007

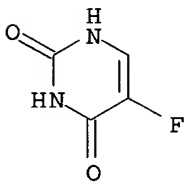
OTHER SOURCE(S): MARPAT 142:423817

AB This invention is directed to potent inhibitors of protein tyrosine kinase such as quinoline/quinoxaline compds. alone or in synergistic combination with antiangiogenic or **chemotherapeutic** agents for the abrogation of mature vasculature within **chemotherapeutic** refractory tumors, pharmaceutical compns. comprising these compds., and to the use of these compds. for treating a patient suffering from or subject to disorders/conditions involving cell proliferation, and particularly treatment of brain cancer, ovarian cancer, pancreatic cancer prostate cancer, and human leukemias, such as chronic myelogenous leukemia, acute myelogenous leukemia or acute lymphoid leukemia.

IT **51-21-8**, Fluorouracil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antivascular and antiproliferation therapy using specific tyrosine kinase inhibitors such as quinoline/quinoxaline compds. in synergistic combination with antiangiogenic and **chemotherapeutic** agents)

RN 51-21-8 CAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI) (CA INDEX NAME)



L26 ANSWER 5 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:371085 CAPLUS

DOCUMENT NUMBER: 142:423814

TITLE: Combination therapy for cancer and viral infections

INVENTOR(S): Moller, Niels Peter Hundahl; Skak, Kresten; Mueller, Jorn Roland

PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.

SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005037306	A1	20050428	WO 2004-DK683	20041008

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

PRIORITY APPLN. INFO.:

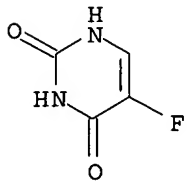
DK 2003-1529	A	20031017
US 2003-513422P	P	20031022
DK 2004-707	A	20040504
US 2004-569566P	P	20040510

AB The invention provides combination treatments with IL-21, analogs and derivs. thereof for the treatment of cancer and viral infection.

IT **51-21-8, 5-Fluorouracil**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy for cancer and viral infections)

RN 51-21-8 CAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 6 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:99470 CAPLUS

DOCUMENT NUMBER: 142:197889

TITLE: Fluoro substituted omega-carboxyaryl diphenyl urea for treatment of raf, VEGFR, PDGFR, p38 and flt-3 kinase-mediated diseases

INVENTOR(S): Dumas, Jacques; Boyer, Stephen; Riedl, Bernd; Wilhelm, Scott

PATENT ASSIGNEE(S): Bayer Pharmaceuticals Corporation, USA

SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005009961	A2	20050203	WO 2004-US23500	20040722
WO 2005009961	A3	20050331		
WO 2005009961	B1	20050602		

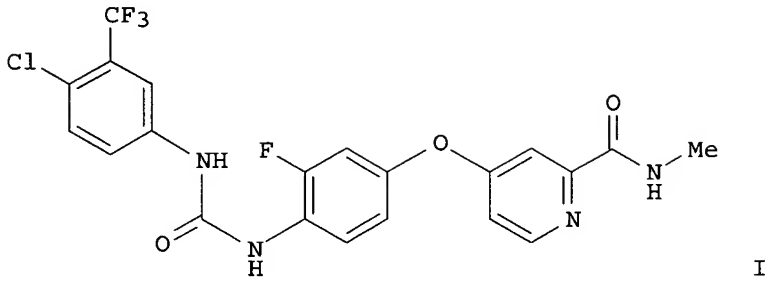
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,

SN, TD, TG

US 2005038080	A1	20050217	US 2004-895985		20040722
PRIORITY APPLN. INFO.:			US 2003-489102P	P	20030723
			US 2004-540326P	P	20040202

GI



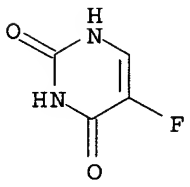
I

AB Title compound I is prepared I and salts thereof is prepared in several steps from 3-fluoro-4-nitrophenol, 4-chloro-N-methylpyridine-2-carboxamide and 4-chloro-3-(trifluoromethyl)phenylisocyanate. I inhibits PDGFR tyrosine kinase with IC50 = 83nM. I is useful for the treatment of, e.g., inflammation and as an antiproliferative agent.

IT **51-21-8, 5-Fluorouracil**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination pharmaceutical; fluoro substituted omega-carboxyaryl di-Ph urea for treatment of raf, VEGFR, PDGFR, p38 and flt-3 kinase-mediated diseases)

RN 51-21-8 CAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI) (CA INDEX NAME)



L26 ANSWER 7 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2005:1078247 CAPLUS
DOCUMENT NUMBER:	143:360086
TITLE:	Combinations of signal transduction inhibitors
INVENTOR(S):	Eck, Stephen Louis; Fry, David William; Leopold, Judith Ann
PATENT ASSIGNEE(S):	Pfizer Inc, USA
SOURCE:	U.S. Pat. Appl. Publ., 31 pp. CODEN: USXXCO
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005222163	A1	20051006	US 2005-95442	20050330
WO 2005094830	A1	20051013	WO 2005-IB720	20050318

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

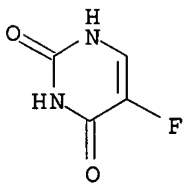
PRIORITY APPLN. INFO.: US 2004-557623P P 20040330

AB The present invention relates to methods for treating cancer comprising utilizing a combination of signal transduction inhibitors. More specifically, the present invention relates to combinations of so called cell cycle inhibitors with mitogen stimulated kinase signal transduction inhibitors, more specifically combinations of CDK inhibitors with mitogen stimulated kinase signal transduction inhibitors, more preferably MEK inhibitors. Other embodiments of the invention relate to addnl. combinations of the aforesaid combinations with standard anti-cancer agents such as cytotoxic agents, palliatives and antiangiogenics. Most specifically this invention relates to combinations of 6-acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8H-pyrido[2,3-d]pyrimidin-7-one including salt forms, which is a selective cyclin-dependent kinase 4 (CDK4) inhibitor, in combination with one or more MEK inhibitors, most preferably N-[(R)-2,3-dihydroxy-propoxy]-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide. The aforementioned combinations are useful for treating inflammation and cell proliferative diseases such as cancer and restenosis.

IT **51-21-8**, 5-FU
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of signal transduction inhibitors)

RN 51-21-8 CAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI) (CA INDEX NAME)



L26 ANSWER 8 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005279135 EMBASE

TITLE: [Tyrosine kinase inhibitors in oncology - Part 2: Clinical applications and perspectives].
TYROSINKINASEINHIBITOREN IN DER TUMORTHERAPIE - TEIL 2: AKTUELLER STAND UND PERSPEKTIVEN.

AUTHOR: Grimm C.F.; Blum H.E.; Geissler M.

CORPORATE SOURCE: Dr. C.F. Grimm, Abteilung Innere Medizin II, Medizinische

Universitatsklinik Freiburg, Hugstetter Strasse 55, 79106 Freiburg, Germany. grimm@med1.ukl.uni-freiburg.de
SOURCE: Deutsche Medizinische Wochenschrift, (10 Jun 2005) Vol. 130, No. 23, pp. 1438-1442.
Refs: 17
ISSN: 0012-0472 CODEN: DMWOAX
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: German
ENTRY DATE: Entered STN: 20050707
Last Updated on STN: 20050707
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 9 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005258464 EMBASE
TITLE: What's new in the treatment of metastatic kidney cancer?.
AUTHOR: Mancuso A.; Sternberg C.N.
CORPORATE SOURCE: C.N. Sternberg, Department of Medical Oncology, San Camillo and Forlanini Hospitals, Circonvallazione Gianicolense, 87, Rome, Italy. csternberg@scamilloforlanini.rm.it
SOURCE: BJU International, (2005) Vol. 95, No. 9, pp. 1171-1180.
Refs: 93
ISSN: 1464-4096 CODEN: BJINFO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050707
Last Updated on STN: 20050707
AB It is important for us as urologists to keep up to date with new drugs being introduced for treating metastatic renal cancer, particularly in the era of the multidisciplinary team approach to cancer therapy. Authors from Rome cover this topic in this month's issue. In other mini reviews in this section, the topics of ejaculatory disorders and cryosurgery are described. Both are relevant to modern management of common urological disorders. Finally there is an historical contribution. There is no such section for these manuscripts, but occasionally subjects of interest are presented which are intended to be of general educational value to the reader. I believe that the paper on prisons presented in this issue to be such a case.

L26 ANSWER 10 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN DUPLICATE 1
ACCESSION NUMBER: 2005308366 EMBASE
TITLE: Current **chemotherapy** options for thymic epithelial neoplasms.
AUTHOR: Papadopoulos K.P.; Thomas Jr. C.R.
CORPORATE SOURCE: Dr. C.R. Thomas Jr., University of Texas Health Science Center, Division of Medical Oncology, Department of Medicine, San Antonio, TX 78229, United States.

cthomas@ctrc.net
SOURCE: Expert Opinion on Pharmacotherapy, (2005) Vol. 6, No. 7, pp. 1169-1177.
Refs: 77
ISSN: 1465-6566 CODEN: EOPHF7
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050805
Last Updated on STN: 20050805
AB Thymomas and thymic carcinoma are rare neoplasms. Surgical resection is the cornerstone of effective therapy. Stage I disease is effectively treated by complete surgical resection. The role of radiation therapy in completely resected stage II disease remains controversial. Adjuvant radiation therapy is useful for local control and may improve survival in patients with incompletely resected tumours. **Cisplatin**-based **chemotherapy** regimens play an important role in the treatment of advanced stage III/IV or recurrent disease thymomas, but have proven less effective for thymic carcinoma. Phase II trials of multimodality therapy incorporating neoadjuvant **chemotherapy**, surgery and postoperative radiation therapy show promise for unresectable disease. This review discusses recent clinical data and the potential role for agents targeting the epidermal growth factor receptor, angiogenesis and apoptotic pathways. .COPYRGT. 2005 Ashley Publications Ltd.

L26 ANSWER 11 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005377689 EMBASE
TITLE: American Society of Clinical Oncology 41st Annual Meeting.
AUTHOR: Dillman R.O.
CORPORATE SOURCE: Dr. R.O. Dillman, Hoag Cancer Center, Bldg. 41, One Hoag Dr., Newport Beach, CA 92658, United States
SOURCE: Expert Opinion on Biological Therapy, (2005) Vol. 5, No. 8, pp. 1117-1127.
Refs: 86
ISSN: 1471-2598 CODEN: EOBTA2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050915
Last Updated on STN: 20050915
AB For many years the annual meeting of the American Society of Clinical Oncology (ASCO) has been the premier meeting in clinical oncology, and one that is closely scrutinised by Wall Street and international investors because of the economic significance of cancer therapies to the pharmaceutical and biotechnology industries. The area of biologicals and targeted therapies exploded in the late 1990s after the blockbuster results with the monoclonal antibody rituximab in the treatment of lymphoma. Although historically a somewhat conservative organisation that is still closely tied to classical cytotoxic **chemotherapy**, ASCO

has been able to integrate various areas of biological therapy into its scope of clinical activity. Although ASCO still has 'American' in its title, it is really the 'International' Society of Clinical Oncology, as reflected by the attendance at this year's meeting by .apprx. 30,000, with approximately two-thirds attending from outside the US. There were 9708 abstracts published in conjunction with the meeting, 86 of which are referenced in this review. There were 10 papers chosen for plenary presentations and many other key papers were presented at other oral abstract sessions and poster discussion session that were organised by tumour type. In addition to key papers submitted by specific tumour type, for this year's meeting there were 103 abstracts published in the session entitled 'Developmental Therapeutics: Immunotherapy', and 218 in the session entitled Developmental Therapeutics: Molecular Targets', for a total of 321 biological therapy abstracts compared with only 125 abstracts for the session entitled 'Developmental Therapeutics: Cytotoxic Therapy'. This meeting review is organised by biotherapy modality rather than tumour type.

L26 ANSWER 12 OF 73 EMBASE

ACCESSION NUMBER: 2005283692 EMBASE
TITLE: Interferon alpha for the treatment of advanced renal cancer.
AUTHOR: Ravaud A.; Dilhuydy M.-S.
CORPORATE SOURCE: A. Ravaud, Hopital Saint-Andre, Department of Medical Oncology and Radiotherapy, CHU Bordeaux, 1 rue Jean Burguet, 33075 Bordeaux Cedex, France. alain.ravaud@chu-bordeaux.fr
SOURCE: Expert Opinion on Biological Therapy, (2005) Vol. 5, No. 6, pp. 749-762.
Refs: 115
ISSN: 1471-2598 CODEN: EOBTA2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
028 Urology and Nephrology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050714
Last Updated on STN: 20050714

AB This paper is an overview on the place of IFN-α in metastatic renal cell carcinoma (MRCC). After a presentation of MRCC and the mode of action of IFN-α, the results of studies including IFN-α alone or in combination with IL-2, **chemotherapy** and other biological modifiers are presented. Finally, new trends for new drugs, including antiangiogenic therapies, are discussed.

L26 ANSWER 13 OF 73 EMBASE

ACCESSION NUMBER: 2005456899 EMBASE
TITLE: Targeted therapies for esophageal cancer.
AUTHOR: Tew W.P.; Kelsen D.P.; Ilson D.H.
CORPORATE SOURCE: Dr. D.H. Ilson, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021, United States. ilsond@mskcc.org
SOURCE: Oncologist, (2005) Vol. 10, No. 8, pp. 590-601.

Refs: 128
ISSN: 1083-7159 CODEN: OCOLF6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20051110
Last Updated on STN: 20051110

AB Esophageal cancer is a highly aggressive neoplasm. In 2005, 14, 520 Americans will be diagnosed with esophageal cancer, and more than 90% will die of their disease. On a global basis, cancer of the esophagus is the sixth leading cause of cancer death worldwide. In fact, gastric and esophageal cancers together accounted for nearly 1.3 million new cases and 980,000 deaths worldwide in 2000-more than lung, breast, or colorectal cancer. Although esophageal squamous cell carcinoma cases have steadily declined, the incidence of gastroesophageal junction adenocarcinoma has increased 4%-10% per year among U.S. men since 1976, more rapidly than for any other cancer type, and parallels rises in population trends in obesity and reflux disease. With advances in surgical techniques and treatment, the prognosis of esophageal cancer has slowly improved over the past three decades. However, the 5-year overall survival rate (14%) remains poor, even in comparison with the dismal survival rates (4%) from the 1970s. The underlying reasons for this disappointingly low survival rate are multifold: (a) ineffective screening tools and guidelines; (b) cancer detection at an advanced stage, with over 50% of patients with unresectable disease or distant metastasis at presentation; (c) high risk for recurrent disease after esophagectomy or definitive chemoradiotherapy; (d) unreliable noninvasive tools to measure complete response to chemoradiotherapy; and (e) limited survival achieved with palliative **chemotherapy** alone for patients with metastatic or unresectable disease. Clearly, additional strategies are needed to detect esophageal cancer earlier and to improve our systemic treatment options. Over the past decade, the field of drug development has been transformed with the identification of and ability to direct treatment at specific molecular targets. This review focuses on novel targeted treatments in development for esophageal squamous cell carcinoma and distal esophageal and gastroesophageal junction adenocarcinoma. .COPYRGT.AlphaMed Press.

L26 ANSWER 14 OF 73 EMBASE

ACCESSION NUMBER: 2005497513 EMBASE
TITLE: Update on angiogenesis inhibitors.
AUTHOR: Zakarija A.; Soff G.
CORPORATE SOURCE: Dr. G. Soff, Division of Hematology/Oncology, Northwestern University, Feinberg School of Medicine, 240 E. Huron Street, Chicago, IL 60611, United States.
g-soff@northwestern.edu
SOURCE: Current Opinion in Oncology, (2005) Vol. 17, No. 6, pp. 578-583.
Refs: 43
ISSN: 1040-8746 CODEN: CUOOE8
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology

036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20051201
Last Updated on STN: 20051201

AB Purpose of review: A number of therapeutic agents have been developed which have anti-angiogenic potential. Here we present the most recent data from clinical trials with some of the promising inhibitors of angiogenesis. Recent findings: Agents that target the vascular endothelial growth factor signaling pathway are the furthest along in clinical development. The last year has brought US Food and Drug Administration approval of bevacizumab (Avastin), a recombinant humanized anti-vascular endothelial growth factor monoclonal antibody. Bevacizumab has demonstrated a survival advantage in combination with **chemotherapy** for patients with metastatic colorectal cancer. Other agents with early promising results include PTK787/ZK 222584 (Vatalanib), ZD6474, and BAY 43-9006 (Sorafenib). Summary: Angiogenesis inhibitors show promise, but evaluation for optimal efficacy has been a problem, given that the mechanisms of action of these agents differ from conventional cytotoxic agents and surrogate markers for inhibition of angiogenesis are not available. .COPYRGT. 2005 Lippincott Williams & Wilkins.

L26 ANSWER 15 OF 73 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 2
ACCESSION NUMBER: 2005:329709 BIOSIS
DOCUMENT NUMBER: PREV200510112099
TITLE: Recent studies in novel therapy for metastatic sarcomas.
AUTHOR(S): Steinert, Dejka M.; Patel, Shreyaskumar R. [Reprint Author]
CORPORATE SOURCE: Univ Texas, MD Anderson Canc Ctr, Dept Sarcoma Med Oncol, Unit 450, 1515 Holcombe Blvd, Houston, TX 77030 USA
spatel@mdanderson.org
SOURCE: Hematology-Oncology Clinics of North America, (JUN 2005) Vol. 19, No. 3, pp. 573-590,VIII,IX-572.
ISSN: 0889-8588.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Aug 2005
Last Updated on STN: 25 Aug 2005

AB Many new **chemotherapeutic** agents and targeted therapies are being studied in the treatment of metastatic soft tissue sarcomas (STSs). This article reviews results of recent clinical studies of gemcitabine, **docetaxel**, **paclitaxel**, ecteinascidin, 9-nitrocamptothecin, and pegylated liposomal **doxorubicin** in patients who have STSs. The use of targeted therapy in STSs is an exciting, constantly changing field. The activity of imatinib mesylate, SU11248, everolimus, and bortezomib are summarized.

L26 ANSWER 16 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005338339 EMBASE
TITLE: News in brief.
SOURCE: Lancet Oncology, (2005) Vol. 6, No. 8, pp. 550.
ISSN: 1470-2045 CODEN: LOANBN
PUBLISHER IDENT.: S 1470-2045(05)70271-0
COUNTRY: United States
DOCUMENT TYPE: Journal; Note

FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
ENTRY DATE: Entered STN: 20050818
Last Updated on STN: 20050818
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 17 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005286253 EMBASE
TITLE: Therapeutic targeting of receptor tyrosine kinases in lung cancer.
AUTHOR: Choong N.W.; Ma P.C.; Salgia R.
CORPORATE SOURCE: Dr. R. Salgia, University of Chicago Medical Center, Pritzker School of Medicine, 5841 S. Maryland Avenue, Chicago, IL 60615, United States. rsalgia@medicine.bsd.uchicago.edu
SOURCE: Expert Opinion on Therapeutic Targets, (2005) Vol. 9, No. 3, pp. 533-559.
Refs: 312
ISSN: 1472-8222 CODEN: EOTTAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050714
Last Updated on STN: 20050714

AB Lung cancer is a difficult illness with a poor overall survival. Even though combination strategies with **chemotherapy**, radiation therapy and surgery have all been utilised, the overall outcome for this disease continues to be relatively disappointing. In order to make a difference in the treatment of lung cancer, novel therapeutics will have to be developed. Through basic biological studies, a number of receptor tyrosine kinases have been implicated in the pathogenesis and progression of lung cancer. In this review, the authors summarise the mechanisms of several major receptor tyrosine kinases in lung cancer, especially epidermal growth factor receptor, Her2/neu, MET, vascular endothelial growth factor and KIT. The biology associated with these receptors is described, and the various novel therapeutic inhibitory strategies that are ongoing in preclinical and clinical studies for lung cancer are detailed. Through understanding of receptor tyrosine kinases and the utilisation of specific inhibitors, it is hopeful that a dramatic impact will be made on the biology and therapy for lung cancer. .COPYRGT. 2005 Ashley Publications Ltd.

L26 ANSWER 18 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005379329 EMBASE
TITLE: Strategies for targeting the multidrug resistance-1 (MDR1)/P-gp transporter in human malignancies.
AUTHOR: Mahadevan D.; Shirahatti N.
CORPORATE SOURCE: D. Mahadevan, University of Arizona Cancer Center, Tucson,

AZ 85724, United States. dmahadevan@azcc.arizona.edu
SOURCE: Current Cancer Drug Targets, (2005) Vol. 5, No. 6, pp. 445-455.
Refs: 66
ISSN: 1568-0096 CODEN: CCDTB
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050922
Last Updated on STN: 20050922

AB ATP-binding cassette (ABC) transporters are a super family of channel proteins that include multidrug resistance 1 (MDR1/P-gp) and multi-drug resistance related proteins (MRPs) whose functions include the efflux of ions, nutrients, lipids, amino acids, peptides, proteins and drugs. The three-dimensional structures of bacterial and human ABC transporters demonstrate that these proteins are ATP-dependent molecular machines that scan the inner membrane leaflet for lipids/drugs and flip them to the outer membrane leaflet. In many human cancers, the level of expression of MDR1 is an important independent prognostic factor that determines response to combination **chemotherapy.** Intrinsic and acquired resistance to **chemotherapy** exposure are due to a high level of MDR1 expression that enhances drug efflux, with associated poor clinical outcome and lower complete remission (CR) rates. Recent clinical trials in hematological and solid malignancies have shown promise for a prolonged remission and improved overall survival when the MDR1 P-gp is inhibited when combined with **chemotherapy.** Structure-based homology modeling of these ABC transporters may help design novel drug candidates to both the membrane-spanning domain (MSD) and the nucleotide-binding domain (NBD) located within the cytoplasm. This review will highlight advances in the utilization of homology modeling in the drug discovery process and how this will impact on fundamental insights to the development of novel therapeutics that could alter and/or inhibit their functions. .COPYRGT. 2005 Bentham Science Publishers Ltd.

L26 ANSWER 19 OF 73 EMBASE
ACCESSION NUMBER: 2005534199 EMBASE
TITLE: Anti-angiogenic strategies in gastrointestinal malignancies.
AUTHOR: Whisenant J.; Bergsland E.
CORPORATE SOURCE: Dr. J. Whisenant, San Francisco Comprehensive Cancer Center, University of California, 1600 Divisadero Street, San Francisco, CA 94115, United States. emilyb@medicine.ucsf.edu
SOURCE: Current Treatment Options in Oncology, (2005) Vol. 6, No. 5, pp. 411-421.
Refs: 96
ISSN: 1527-2729 CODEN: CTOOBW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20051208
Last Updated on STN: 20051208

AB Advances in our understanding of the mechanisms underlying tumor progression suggest that angiogenesis plays a key role in gastrointestinal malignancies. Vascular endothelial growth factor (VEGF) has emerged as an important therapeutic target, and a variety of strategies to inhibit VEGF are under investigation. The approval of bevacizumab for use in patients with previously untreated metastatic colorectal cancer was based on clinical data suggesting that VEGF is a valid therapeutic target in this disease. As the data mature from ongoing trials, the role of angiogenesis inhibitors in the treatment of colon cancer and other gastrointestinal malignancies will be more clearly defined. Additional information is needed to identify the diseases and stages most likely to benefit from anti-angiogenic agents and the optimal sequences and therapeutic combinations that should be studied.

L26 ANSWER 20 OF 73 EMBASE
ACCESSION NUMBER: 2005244544 EMBASE
TITLE: [Angiogenesis and anti-angiogenic strategies for glioblastomas].
ANGIOGENESE ET STRATEGIES ANTI-ANGIOGENIQUES DES GLIOBLASTOMES.
AUTHOR: De Bouard S.; Guillamo J.-S.
CORPORATE SOURCE: S. De Bouard, Groupe Regional d'Etude sur le Cancer (Grecan), Universite de Caen Basse-Normandie, Centre Francois-Baclesse, avenue du General-Harris, 14076 Caen Cedex 05, France. s.de.bouard@baclesse.fr
SOURCE: Bulletin du Cancer, (2005) Vol. 92, No. 4, pp. 360-372.
Refs: 153
ISSN: 0007-4551 CODEN: BUCABS
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: French
SUMMARY LANGUAGE: English; French
ENTRY DATE: Entered STN: 20050616
Last Updated on STN: 20050616

AB The poor prognosis of patients with glioblastoma multiforme in spite of aggressive conventional anticancer therapies has led to the search for new therapeutic strategies. As glioblastomas are highly vascularized and their growth is angiogenesis-dependent, the inhibition of the sprouting of new capillaries from preexisting blood vessels is one of the most promising therapeutic approaches. Different anti-angiogenic strategies have been developed: inhibition of pro-angiogenic factors and/or receptors and/or downstream cell signaling, inactivation of endothelial cells, inhibition of cellular adhesion molecules and/or extracellular matrix remodeling. Inhibitors of angiogenesis are separated into endogenous inhibitors such as angiostatin, trombospondin or alpha interferon and natural or synthetic inhibitors such as thalidomide, antibodies against angiogenic growth factors or inhibitors of tyrosine kinase receptors. In this review, the majority of experimental studies in glioblastoma models in vivo are summarized and clinical perspectives are discussed.

L26 ANSWER 21 OF 73 EMBASE

reserved on STN
ACCESSION NUMBER: 2005534194 EMBASE
TITLE: Promising systemic therapy for renal cell carcinoma.
AUTHOR: Cooney M.M.; Remick S.C.; Vogelzang N.J.
CORPORATE SOURCE: Dr. N.J. Vogelzang, Nevada Cancer Institute, University of Nevada School of Medicine, Las Vegas, NV 89135, United States. nvogelza@nvcancer.org
SOURCE: Current Treatment Options in Oncology, (2005) Vol. 6, No. 5, pp. 357-365.
Refs: 44
ISSN: 1527-2729 CODEN: CTOOBW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20051208
Last Updated on STN: 20051208

AB In the United States, advanced kidney cancer accounts for over 12,000 deaths each year. Immunotherapy with either interferon or interleukin-2 (IL-2) has been the standard of care for over two decades. High-dose IL-2 can apparently cure 10% to 15% of patients treated, but due to the required inpatient care and the attendant toxicities, it is only administered to less than 1000 patients per year in the United States (Chiron, personal communication). Interferon is a less active agent than IL-2 but it has still been shown to be superior to therapy with either megesterol or vinblastine. Interferon typically resutts in very few long-term responses and is given to most patients with metastatic kidney cancer. Median survival after interferon therapy is dependent on risk group but is typically 12 to 15 months. Thus, new therapies are urgently needed in this refractory disease. Novel compounds currently being tested in clinical trials are showing promise in advanced kidney cancer. The molecular targets of these drugs include interfering with the vascular endothelial growth factor receptors or the raf kinase pathway, angiogenesis inhibition, and antimicrotubule agents. A review of the preclinical and early clinical development of some of these novel compounds will be discussed. Copyright .COPYRGT. 2005 by Current Science Inc.

L26 ANSWER 22 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005275679 EMBASE
TITLE: Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy.
AUTHOR: Ferrara N.; Hillan K.J.; Novotny W.
CORPORATE SOURCE: N. Ferrara, Department of Molecular Oncology, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, United States. nf@gene.com
SOURCE: Biochemical and Biophysical Research Communications, (29 Jul 2005) Vol. 333, No. 2, pp. 328-335.
Refs: 96
ISSN: 0006-291X CODEN: BBRCA
PUBLISHER IDENT.: S 0006-291X(05)01134-4
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050714
Last Updated on STN: 20050714

AB Vascular endothelial growth factor (VEGF) is an endothelial cell-specific mitogen in vitro and an angiogenic inducer in vivo. The tyrosine kinases Flt-1 (VEGFR-1) and Flk-1/KDR (VEGFR-2) are high affinity VEGF receptors. VEGF plays an essential role in developmental angiogenesis and is important also for reproductive and bone angiogenesis. Substantial evidence also implicates VEGF as a mediator of pathological angiogenesis. Anti-VEGF monoclonal antibodies and other VEGF inhibitors block the growth of several tumor cell lines in nude mice. Clinical trials with VEGF inhibitors in a variety of malignancies are ongoing. Recently, a humanized anti-VEGF monoclonal antibody (bevacizumab; Avastin) has been approved by the FDA as a first-line treatment for metastatic colorectal cancer in combination with **chemotherapy.** Furthermore, VEGF is implicated in intraocular neovascularization associated with diabetic retinopathy and age-related macular degeneration.

L26 ANSWER 23 OF 73 EMBASE
ACCESSION NUMBER: 2005319850 EMBASE
TITLE: Targeted therapy for colorectal cancer: Mapping the way.
AUTHOR: Mocellin S.; Lise M.; Nitti D.
CORPORATE SOURCE: S. Mocellin, Department of Oncological and Surgical Sciences, University of Padova, Via Giustiniani 2, 35128 Padova, Italy. mocellins@hotmail.com
SOURCE: Trends in Molecular Medicine, (2005) Vol. 11, No. 7, pp. 327-335.
Refs: 75
ISSN: 1471-4914 CODEN: TMMRCY
PUBLISHER IDENT.: S 1471-4914(05)00113-9
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050811
Last Updated on STN: 20050811

AB In spite of the significant advances in conventional therapeutic approaches to colorectal cancer (CRC), most patients ultimately die of their disease. Dissecting the molecular mechanisms underlying CRC progression will not only accelerate the development of novel cancer-selective drugs but will also enable the therapeutic regimen to be personalized according to the molecular features of individual patients and tumors. Here, we report on the novel insights into CRC biology that are paving the way to the development of molecular therapies and summarize the results from recent clinical trials demonstrating that agents targeting tumor-specific molecular derangements can significantly improve the therapeutic efficacy of conventional **chemotherapy.** Only a broader clinical implementation of these concepts will provide patients

with CRC the best chance of a cure. .COPYRGT. 2005 Elsevier Ltd. All rights reserved.

L26 ANSWER 24 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005243920 EMBASE
TITLE: Clinical significance of VEGF-A, -C and -D expression in esophageal malignancies.
AUTHOR: Kleespies A.; Bruns C.J.; Jauch K.-W.
CORPORATE SOURCE: Dr. A. Kleespies, Chirurgische Klinik und Poliklinik, Klinikum Grosshadern, Ludwig-Maximilians-Universitat Munchen, Marchioninistrasse 15, 81377 Munchen, Germany. axelkleespies@aol.com
SOURCE: Onkologie, (2005) Vol. 28, No. 5, pp. 281-288.
Refs: 92
ISSN: 0378-584X CODEN: ONKOD2
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English; German
ENTRY DATE: Entered STN: 20050616
Last Updated on STN: 20050616

AB Vascular endothelial growth factors (VEGF)-A, -C and -D are members of the proangiogenic VEGF family of glycoproteins. VEGF-A is known to be the most important angiogenic factor under physiological and pathological conditions, while VEGF-C and VEGF-D are implicated in the development and sprouting of lymphatic vessels, so called lymphangiogenesis. Local tumor progression, lymph node metastases and hematogenous tumor spread are important prognostic factors for esophageal carcinoma (EC), one of the most lethal malignancies throughout the world. We found solid evidence in the literature that VEGF expression contributes to tumor angiogenesis, tumor progression and lymph node metastasis in esophageal squamous cell carcinoma (SCC), and many authors could show a prognostic value for VEGF-assessment. In adenocarcinoma (AC) of the esophagus angiogenic properties are acquired in early stages, particularly in precancerous lesions like Barrett's dysplasia. However, VEGF expression fails to give prognostic information in AC of the esophagus. VEGF-C and -D were detected in SCC and dysplastic lesions, but not in normal mucosa of the esophagus. VEGF-C expression might be associated with lymphatic tumor invasion, lymph node metastases and advanced disease in esophageal SCC and AC. Therapeutic interference with VEGF signaling may prove to be a promising way of anti-angiogenic co-treatment in esophageal carcinoma. However, concrete clinical data are still pending. .COPYRGT. 2005 S. Karger GmbH.

L26 ANSWER 25 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005276492 EMBASE
TITLE: Bevacizumab extends survival for patients with nonsquamous non-small-cell lung cancer.
AUTHOR: Belani C.P.; Ramalingam S.
CORPORATE SOURCE: Dr. C.P. Belani, University of Pittsburgh School of Medicine, Lung and Thoracic Cancer Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA, United States
SOURCE: Clinical Lung Cancer, (2005) Vol. 6, No. 5, pp. 267-268.
Refs: 3

ISSN: 1525-7304 CODEN: CLCLCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 006 Internal Medicine
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20050707
Last Updated on STN: 20050707
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 26 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005263172 EMBASE
TITLE: **Chemotherapy** for metastatic NSCLC: Current status and future direction.
AUTHOR: Govindan R.
CORPORATE SOURCE: Prof. R. Govindan, Washington University, Medical School, Division of Oncology, 660 South Euclid Avenue, St. Louis, MO 63110, United States. rgovinda@im.wustl.edu
SOURCE: Nature Clinical Practice Oncology, (2005) Vol. 2, No. 5, pp. 238-239.
Refs: 5
ISSN: 1743-4254
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20050630
Last Updated on STN: 20050630
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 27 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005194874 EMBASE
TITLE: Molecular markers, molecular-targeted therapies and taxanes: How to integrate the progress into clinical research and practice for the management of head and neck cancers.
AUTHOR: Awada A.; Lalami Y.
CORPORATE SOURCE: Dr. A. Awada, Jules Bordet Institute, Boulevard de Waterloo, 121, B-1000 Brussels, Belgium. ahmad.awada@bordet.be
SOURCE: Current Opinion in Oncology, (2005) Vol. 17, No. 3, pp. 209-211.
Refs: 13
ISSN: 1040-8746 CODEN: CUOOE8
COUNTRY: United States
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 011 Otorhinolaryngology
014 Radiology
016 Cancer
037 Drug Literature Index

038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20050616
Last Updated on STN: 20050616
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 28 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005477421 EMBASE
TITLE: Biology, diagnosis and therapeutic options in gastrointestinal stromal tumours.
AUTHOR: Comandone A.; Boglione A.
CORPORATE SOURCE: A. Comandone, Oncologia Medica, Ospedale Gradenigo, C.so Regina Margherita 8, 10153 Torino, Italy. alessandro.comandone@h-gradenigo.it
SOURCE: Minerva Chirurgica, (2005) Vol. 60, No. 4, pp. 197-203. Refs: 18
ISSN: 0026-4733 CODEN: MICHAH
COUNTRY: Italy
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English; Italian
ENTRY DATE: Entered STN: 20051117
Last Updated on STN: 20051117
AB Gastrointestinal stromal tumours (GIST) are the most common form of mesenchymal tumour of the intestinal tract. The incidence in Italy is approximately 800-1 400 new cases/year; the most common localization is the stomach (50-60%), small bowel (20-30%), rectum (10%) and esophagus (5%). Extra-abdominal localizations are very rare. GIST characteristically express the Kit protein, a transmembrane tyrosine kinase receptor for the specific ligand. Most GIST have a mutation in kit receptor which becomes constitutive for the neoplasm. Kit mutation is a early tumorogenesis event. The disease clinically can present as an occasionally finding or can be diagnosed after hemorrage, perforation or obstruction of the gastrointestinal tract. Surgery is the mainstay of the therapy mainly in primary tumour. More debated is its role in metastatic disease. In this situation imatinib mesilate, a tyrosine kinase inhibitor, is the drug of choice which has changed the natural history of the disease. Metastatic GIST before imatinib mesilate discovery had 6 months survival, now in the 3 published studies after 3 years of follow-up, median survival has not already reached. New drugs are now under evaluation in order to prolong the pharmacological activity of tyrosine kinase inhibition after progression of the disease.

L26 ANSWER 29 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005463709 EMBASE
TITLE: Anticancer therapeutics: "Addictive" targets, multi-targeted drugs, new drug combinations.
AUTHOR: Broxterman H.J.; Georgopapadakou N.H.
CORPORATE SOURCE: H.J. Broxterman, Department of Medical Oncology, Vrije Universiteit Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands. H.Broxterman@VUmc.nl
SOURCE: Drug Resistance Updates, (2005) Vol. 8, No. 4, pp. 183-197. Refs: 168
ISSN: 1368-7646 CODEN: DRUPFW

PUBLISHER IDENT.: S 1368-7646(05)00068-3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20051128
Last Updated on STN: 20051128

AB The annual meeting of the American Association for Cancer Research (AACR) provided a panoramic view of new developments and trends in cancer research. In the area of new drug development, a recurrent theme was receptor tyrosine kinase (TK) inhibitors, with multitargeted, small molecule inhibitors - highly potent against a family of receptors such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor (PDGFR) and the receptor tyrosine kinase KIT - taking centre stage. Several agents interfering with intracellular targets that are components of key oncogenic signaling pathways, such as RAF kinase, phosphatidylinositol 3-kinase (PI3K)/Akt or Src, are in preclinical and early clinical development. "Addictive" targets, such as the Bcr-Abl fusion protein in chronic myeloid leukemia (CML), are critical for maintaining the malignant phenotype and hence represent an Achilles' heel for selective drugs. Significantly, novel targeted therapeutics currently in clinical development do not generally lead to cures or long-term survival for most intractable cancers; resistance may eventually develop. Anti-metastatic agents and anti-adhesion drugs, which collectively act on tumor cell-stroma interactions (anti-stromal therapy), are also actively pursued. In addition, forms of cell death other than apoptosis - cellular senescence, cancer cell-specific cell-cycle processes and the hypoxic environment - are being explored in order to identify novel targets for more selective therapy. This report also highlights developments aimed at more safe and effective drug combinations. Evaluating drug combinations, and elucidating the rationale for combinations of old (cytotoxic) and new (biological) anticancer agents, are promising research areas and taxane-based combinations are presented as examples. The report is based on presentations at AACR 2005 and related publications of the first half of 2005. .COPYRGT. 2005 Elsevier Ltd. All rights reserved.

ACCESSION NUMBER: 2005393160 EMBASE
TITLE: Novel treatments for metastatic renal cell carcinoma.
AUTHOR: Van Spronsen D.J.; Mulders P.F.A.; De Mulder P.H.M.
CORPORATE SOURCE: D.J. Van Spronsen, Department of Medical Oncology 550, Radboud University, Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, Netherlands. d.vanspronsen@onco.umcn.nl
SOURCE: Critical Reviews in Oncology/Hematology, (2005) Vol. 55, No. 3, pp. 177-191.
Refs: 154
ISSN: 1040-8428 CODEN: CCRHEC
PUBLISHER IDENT.: S 1040-8428(05)00096-X
COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20051006
Last Updated on STN: 20051006

AB The mainstay of any curative treatment in renal cell carcinoma (RCC) is surgery. In case of metastatic disease at presentation a radical nephrectomy is recommended to good performance status patients prior to start of interferon-alfa treatment. Interferon-α (IFN-α) offers in a small but significant percentage of patients advantage in overall survival; interleukin-2 (IL-2) based therapy gives similar survival rates. To date hormonal and **chemotherapy** do not have a proven impact on survival. The recent new insights in the molecular biology of clear RCC has revealed a key-role for vascular endothelial growth factor (VEGF) in the stimulation of angiogenesis in this highly vascularized tumour. This opens interesting new treatment strategies including: blockage of VEGF with the monoclonal antibody bevacizumab and inhibition of VEGF receptor tyrosine kinases (with small oral molecules such as SU11248 or PTK787). Likewise, inhibition of the Raf kinase pathway (with oral Bay 43-9006) or inhibition of the mTOR pathway (with i.v. CCI-779) are under investigation. Preliminary clinical results with all these compounds are interesting and the results of ongoing phase III studies will become available in the next years.

L26 ANSWER 31 OF 73 EMBASE
ACCESSION NUMBER: 2005217983 EMBASE
TITLE: Second-line therapy for advanced colorectal carcinoma.
AUTHOR: Starling N.; Cunningham D.
CORPORATE SOURCE: N. Starling, Gastrointestinal Unit, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, United Kingdom
SOURCE: Current Oncology Reports, (2005) Vol. 7, No. 3, pp. 173-180.
Refs: 49
ISSN: 1523-3790 CODEN: CORUAT
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
017 Public Health, Social Medicine and Epidemiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050602
Last Updated on STN: 20050602

AB The past decade has witnessed considerable advances in the treatment of colorectal cancer (CRC). The emergence and integration into clinical practice of new cytotoxic agents, such as **irinotecan** and oxaliplatin, has had a significant impact on outcomes from advanced CRC with median survivals of 18 to 21 months now achievable. Improvements in survival as a consequence of using these drugs as salvage therapies ultimately led to demonstration of efficacy for both in the first-line treatment of CRC. As the importance of second-line therapy is increasingly recognized, key issues, such as optimal schedules, **chemotherapy** combinations, and sequential therapy, need to be addressed. The integration of newer biologic agents, such as cetuximab and bevacizumab, for which recent data have emerged, has further added to the complexities of delivering therapy to patients with advanced CRC, heralding a new treatment era for this disease.

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ACCESSION NUMBER: 2005117653 EMBASE
TITLE: Anti-angiogenic therapy as a cancer treatment paradigm.
AUTHOR: Dhanabal M.; Jeffers M.; LaRochelle W.J.
CORPORATE SOURCE: M. Dhanabal, CuraGen Corporation, 322 East Main Street, Branford, CT 06405, United States. mdhanabal@curagen.com
SOURCE: Current Medicinal Chemistry - Anti-Cancer Agents, (2005) Vol. 5, No. 2, pp. 115-130.
Refs: 193
ISSN: 1568-0118 CODEN: CMCACI
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
021 Developmental Biology and Teratology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050324
Last Updated on STN: 20050324

AB The inhibition of angiogenesis is an emerging therapeutic strategy for cancer treatment. In contrast to conventional therapies, anti-angiogenic therapies primarily target tumor-associated endothelial cells which serve as a lifeline for tumor growth, progression and metastasis. By blocking the supply of essential nutrients and the removal of metabolites, anti-angiogenic therapies aim to delay both primary and metastatic tumor growth while overcoming the inherent cytotoxicities of classical **chemotherapies.** Indeed, tumor-related angiogenesis is a multi-step process initiated by a cascade of proangiogenic factors secreted from both the tumor and host tissues. These intricate processes involve a close interaction of tumor and associated endothelial cells as well as an intimate communication between proliferating endothelial cells, stromal cells and extracellular matrix components. Inhibition of these proangiogenic mechanisms has become a major challenge for the development of anti-cancer treatment modalities. In this regard, anti-angiogenic therapies embody a potentially powerful adjunct to traditional cancer therapies. In this review, we provide an overview of traditional anti-cancer drugs and discuss the fundamentals of anti-angiogenic therapies. While presenting the salient features of the anti-angiogenic agents targeting the individual phases of angiogenesis, we highlight the potential for specific agent development as novel anti-angiogenic therapeutics. Finally, we present and summarize emerging angiogenesis inhibitors. .COPYRGT. 2005 Bentham Science Publishers Ltd.

L26 ANSWER 33 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005213682 EMBASE
TITLE: Targeted therapy for hematologic malignancies.
AUTHOR: Kuriakose P.
CORPORATE SOURCE: Dr. P. Kuriakose, Department of Internal Medicine, Division of Hematology/Oncology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, United States. pkuriak1@hfhs.org
SOURCE: Cancer Control, (2005) Vol. 12, No. 2, pp. 82-90.
Refs: 129

ISSN: 1073-2748 CODEN: CACOFD
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 023 Nuclear Medicine
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050602
Last Updated on STN: 20050602

AB Background: The introduction of monoclonal antibodies, either as native molecules or conjugated to radioisotopes or other toxins, has led to new therapeutic options for patients with hematologic malignancies. In addition, the use of small molecules against specific cell surface receptors, enzymes, and proteins has become an important strategy in the treatment of such disorders. Methods: The author reviewed the published clinical trials of monoclonal antibody and other targeted therapies in hematologic malignancies. Results: Results from several trials demonstrate a therapeutic benefit for the use of monoclonal antibodies (either native or conjugated) and other targeted therapies, used alone or in combination with standard cytotoxic **chemotherapy.** Conclusions: Targeted therapy of hematologic malignancies seems to be an effective and less toxic approach to the treatment of such disorders. Nevertheless, additional studies are needed to determine where and when such management fits into a therapeutic regimen for any given disorder, whether upfront or as salvage therapy, alone or in combination with **chemotherapy** (concurrent or sequential).

L26 ANSWER 34 OF 73 EMBASE

ACCESSION NUMBER: 2005257092 EMBASE
TITLE: Platelet-derived growth factor receptor (PDGFR): A target for anticancer therapeutics.
AUTHOR: Board R.; Jayson G.C.
CORPORATE SOURCE: R. Board, Cancer Research UK Department Medical Oncology, Christie Hospital, Manchester M20 4BX, United Kingdom. Ruth.Board@christie-tr.nwest.nhs.uk
SOURCE: Drug Resistance Updates, (2005) Vol. 8, No. 1-2, pp. 75-83. Refs: 80
ISSN: 1368-7646 CODEN: DRUPFW
PUBLISHER IDENT.: S 1368-7646(05)00026-9
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050630
Last Updated on STN: 20050630

AB Platelet-derived growth factors (PDGFs) and their tyrosine kinase receptors (PDGFRs) have been implicated in the pathogenesis of a number of tumor types and play an important role in angiogenesis. Tumor growth can be promoted by PDGF via autocrine stimulation of malignant cells, by overexpression or overactivation of PDGFRs, or by stimulation of angiogenesis within the tumor. These mechanisms could provide possible

therapeutic targets. PDGFR blockade may also lower the interstitial fluid pressure within solid tumors and enhance drug delivery. Here we discuss the possible therapeutic roles of PDGFR antagonists in the treatment of cancer, alone and in combination with **chemotherapy** or other targeted agents. Extensive experimental data highlight the potential therapeutic advantage of targeting PDGFR. However, recent clinical data suggest that antagonism of this growth factor is associated with fluid accumulation that could obscure any clinical benefit. Further clinical research is required to optimise inhibition of this cytokine-receptor system.

L26 ANSWER 35 OF 73 EMBASE

ACCESSION NUMBER: 2005213681 EMBASE
TITLE: Molecularly targeted therapies for breast cancer.
AUTHOR: Hobday T.J.; Perez E.A.
CORPORATE SOURCE: Dr. E.A. Perez, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, United States. perez.edith@mayo.edu
SOURCE: Cancer Control, (2005) Vol. 12, No. 2, pp. 73-81.
Refs: 51
ISSN: 1073-2748 CODEN: CACOFD
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050602
Last Updated on STN: 20050602

AB Background: The management of patients with localized and advanced breast cancer continues to evolve. **Chemotherapy**, endocrine therapy, and trastuzumab are effective therapies but leave considerable room for improvement. As the cellular aberrations inherent to cancer cells in general and breast cancer cells specifically are better understood, therapies to target specific cellular pathways continue to be developed with the goal of expanding available effective therapy through better patient selection. Methods: We conducted a computerized search of the medical literature as well as a manual search of selected meeting abstracts. Results: Several targeted therapies are in phase III clinical trials testing their promise in the treatment of breast cancer. Many other agents are completing phase I and II testing. An overview of the most promising agents in clinical development is discussed herein. Conclusions: Targeted therapy for breast cancer is a reality at this time, and several new agents hold promise for expanding and refining the pool of patients likely to further benefit from this approach in the near future.

L26 ANSWER 36 OF 73 EMBASE

ACCESSION NUMBER: 2005178866 EMBASE
TITLE: Acute abdomen due to perforated stromal tumor of small intestine (case report).
AUTHOR: Efremidou H.I.; Lyratzopoulos N.; Romanidis K.; Manolas K.J.; Minopoulos G.J.
CORPORATE SOURCE: H.I. Efremidou, 1st Department of Surgery, Demokritus University of Thrace, Univ. Gen. Hosp. of Alexandroupolis, Alexandroupolis, Greece
SOURCE: Surgical Chronicles, (2005) Vol. 10, No. 1, pp. 53-58.
Refs: 28

ISSN: 1108-5002
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 009 Surgery
016 Cancer
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: Greek
SUMMARY LANGUAGE: Greek; English
ENTRY DATE: Entered STN: 20050505
Last Updated on STN: 20050505

AB Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. It was discovered that they express the receptor tyrosine kinase KIT (CD117). GISTs often present with vague symptoms depending on size, location and histological type of the tumor, but it is possible, sometimes to cause clinical symptoms and signs of acute abdomen (gastrointestinal bleeding, obstruction, perforation). GISTs had been observed to be relatively resistant to standard **chemotherapy.** Imatinib, which is a relatively selective and competitive inhibitor of c-KIT, is the first effective systemic therapy for metastatic and locally irresectable GISTs. A case of perforated gastrointestinal stromal tumor(GIST) of small intestine causing acute abdomen is described with a brief overview of the available literature.

L26 ANSWER 37 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005095913 EMBASE
TITLE: [Anti-angiogenic agents in cancerology: Myth or reality?].
LES ANTI-ANGIOGENIQUES EN CANCEROLOGIE: MYTHE OU REALITE?.
AUTHOR: Armand J.-P.
CORPORATE SOURCE: J.-P. Armand, Departement de Medecine, Institut Gustave Roussy, 39, rue Camille Desmoulins, F94800 Villejuif, France
SOURCE: Annales Pharmaceutiques Francaises, (2005) Vol. 63, No. 1, pp. 25-27.
Refs: 8
ISSN: 0003-4509 CODEN: APFRAD
COUNTRY: France
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
039 Pharmacy
LANGUAGE: French
ENTRY DATE: Entered STN: 20050317
Last Updated on STN: 20050317
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 38 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005257087 EMBASE
TITLE: Tyrosine kinase inhibitor resistance in cancer: Role of ABC multidrug transporters.
AUTHOR: Ozvegy-Laczka C.; Cserepes J.; Elkind N.B.; Sarkadi B.
CORPORATE SOURCE: B. Sarkadi, National Medical Center, Institute of Haematology and Immunology, Membrane Research Group of the Hungarian Academy of Sciences, Dioszegi u. 64, H-1113 Budapest, Hungary. sarkadi@biomembrane.hu
SOURCE: Drug Resistance Updates, (2005) Vol. 8, No. 1-2, pp. 15-26.
Refs: 120
ISSN: 1368-7646 CODEN: DRUPFW

PUBLISHER IDENT.: S 1368-7646(05)00018-X
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050630
Last Updated on STN: 20050630

AB Recent antitumor drug research has seen the development of a large variety of tyrosine kinase inhibitors (TKIs) with increasing specificity and selectivity. These are highly promising agents for specific inhibition of malignant cell growth and metastasis. However, their therapeutic potential also depends on access to their intracellular targets, which may be significantly affected by certain ABC membrane transporters. It has been recently shown that several human multidrug transporter ABC proteins interact with specific TKIs, and the ABCG2 transporter has an especially high affinity for some of these kinase inhibitors. These results indicate that multidrug resistance protein modulation by TKIs may be an important factor in the treatment of cancer patients; moreover, the extrusion of TKIs by multidrug transporters may result in tumor cell TKI resistance. Interaction with multidrug resistance ABC transporters may also significantly modify the pharmacokinetics and toxicity of TKIs in patients.

L26 ANSWER 39 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005446953 EMBASE
TITLE: Anti-VEGF therapy in renal cell carcinoma, breast cancer, and lung cancer.
AUTHOR: Gordon M.S.
CORPORATE SOURCE: Dr. M.S. Gordon, Department of Medicine, University of Arizona College of Medicine, Phoenix, AZ, United States
SOURCE: Clinical Advances in Hematology and Oncology, (2005) Vol. 3, No. 7 SUPPL. 7, pp. 8-9.
Refs: 8
ISSN: 1543-0790
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
028 Urology and Nephrology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20051020
Last Updated on STN: 20051020
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 40 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005446950 EMBASE
TITLE: Antiangiogenesis: Implications for the treatment of solid tumor malignancies. Part 1 of a 3-part series: Targeting VEGF - Current and future research directions.
AUTHOR: Ellis L.M.; Hecht J.R.; Gordon M.S.
CORPORATE SOURCE: Dr. L.M. Ellis, Department of Surgical Oncology and Cancer Biology, University of Texas M. D. Anderson Cancer Center,

Houston, TX, United States
SOURCE: Clinical Advances in Hematology and Oncology, (2005) Vol. 3, No. 7 SUPPL. 7, pp. 1-3.
ISSN: 1543-0790
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20051020
Last Updated on STN: 20051020

AB Angiogenesis produces new blood vessel growth in tumors. Vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) play a major role in tumor angiogenesis, prompting the development of biologic therapies against these factors. Antiangiogenic therapies, whether monoclonal antibodies or small molecule inhibitors, appear to act via multiple mechanisms to regulate tumor vasculature as well as to act upon tumor cells directly. These agents have been tested in a variety of cancers with good results. A monoclonal antibody against VEGF, bevacizumab, has been shown to increase the efficacy of several **chemotherapeutic** regimens in metastatic colorectal cancer, and has been approved for first-line use in combination with 5-**fluorouracil**-based **chemotherapy.** In addition, bevacizumab has shown promise in phase II trials in renal cell carcinoma and phase III trials in non-small cell lung cancer, and it is being tested in breast cancer. Small molecule inhibitors of VEGFRs have also been extensively studied in colorectal cancer and renal cell carcinoma. Phase III studies of the VEGFR antagonist PTK787/ZK222584 in colorectal cancer are ongoing but initial analysis did not demonstrate a benefit of the addition of this agent to FOLFOX. BAY 43-9006, a dual-action Raf kinase and VEGFR inhibitor, as well as SU11248 and AG-013736, which are VEGFR and platelet-derived growth factor receptor inhibitors, have been tested in renal cell carcinoma with encouraging results. Future studies will clarify the role of the biologics in these diseases and will focus on the best dose, schedule, and therapeutic combinations.

L26 ANSWER 41 OF 73 EMBASE

ACCESSION NUMBER: 2005290872 EMBASE
TITLE: Role of novel targeted therapies in the clinic.
AUTHOR: Herbst R.S.
CORPORATE SOURCE: Dr. R.S. Herbst, Department of Thoracic/Head and Neck Medical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4009, United States. rherbst@mdanderson.org
SOURCE: British Journal of Cancer, (2005) Vol. 92, No. SUPPL. 1, pp. S21-S27.
Refs: 62
ISSN: 0007-0920 CODEN: BJCAAI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050714
Last Updated on STN: 20050714

AB The number and variety of novel, molecular-targeted agents offers realistic hope for significant advances in cancer treatment. The potential of these new treatment approaches is unquestionable, but the reality is something that only thorough clinical evaluation and experience can reveal. Clinical experience of targeted therapies is at an early stage but it is likely that we will have an increasing number of treatment options available to us in the near future. This manuscript explores our current understanding of molecular-targeted therapies and considers: What approach should be used? (single vs multitarget agents); When should they be administered? (identifying the optimal point for intervention); How should they be used? (monotherapy or combination therapy regimens); and Who should we be giving them to? (acknowledging the need for patient selection). .COPYRGT. 2005 Cancer Research UK.

L26 ANSWER 42 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005454831 EMBASE
TITLE: [Urological cancers excluding prostate cancer].
CANCERS UROLOGIQUES A L'EXCLUSION DU CANCER DE LA PROSTATE.
AUTHOR: Medioni J.; Oudard S.
CORPORATE SOURCE: J. Medioni, Departement d'Oncologie Medicale, Hopital Europeen Georges Pompidou, 20 rue Leblanc, F-75015 Paris, France. jacques.medioni@egp.aphp.fr
SOURCE: Oncologie, (2005) Vol. 7, No. 4 SUPPL., pp. NS33-NS36.
ISSN: 1292-3818 CODEN: OOLOFG
COUNTRY: France
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: French
ENTRY DATE: Entered STN: 20051103
Last Updated on STN: 20051103
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 43 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005454834 EMBASE
TITLE: [The target therapies].
LES THERAPEUTIQUES CIBLEES.
AUTHOR: Fayette J.
CORPORATE SOURCE: J. Fayette, Hopital Edouard Herriot, Service d'Oncologie Medicale, Pavillon E, 5, place d'Arsonval, F-69003 Lyon, France
SOURCE: Oncologie, (2005) Vol. 7, No. 4 SUPPL., pp. NS47-NS49.
ISSN: 1292-3818 CODEN: OOLOFG
COUNTRY: France
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: French
ENTRY DATE: Entered STN: 20051103
Last Updated on STN: 20051103
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 44 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:965067 CAPLUS

DOCUMENT NUMBER: 141:406039
TITLE: Combinations for the treatment of diseases involving cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis
INVENTOR(S): Hilberg, Frank; Solca, Flavio; Stefanic, Martin Friedrich; Baum, Anke; Munzert, Gerd; Van Meel, Jacobus C. A.
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004096224	A2	20041111	WO 2004-EP4363	20040424
WO 2004096224	A3	20041216		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1473043	A1	20041103	EP 2003-9587	20030429
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

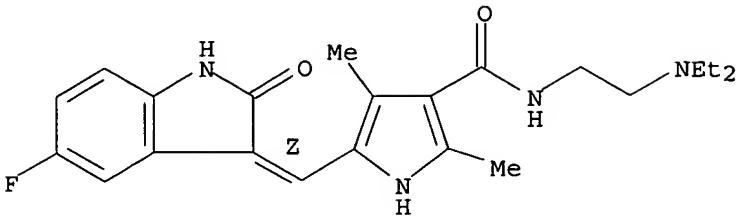
PRIORITY APPLN. INFO.:
EP 2003-9587 A 20030429
EP 2004-508 A 20040113
EP 2004-1171 A 20040121

AB The present invention relates to a pharmaceutical combination for the treatment of diseases which involves cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. The invention also relates to a method for the treatment of said diseases, comprising co-administration of effective amts. of specific active compds. and/or co-treatment with radiation therapy, in a ratio which provides an additive and synergistic effect, and to the combined use of these specific compds. and/or radiotherapy for the manufacture of corresponding pharmaceutical combination prepns. The pharmaceutical combination can include selected protein tyrosine kinase receptor antagonists and further **chemotherapeutic** or naturally occurring semisynthetic or synthetic agents.

IT **557795-19-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SU 11248; drug combinations for diseases involving cell proliferation and migration or apoptosis or angiogenesis including protein tyrosine kinase receptor antagonists and radiotherapy)

RN 557795-19-4 CAPLUS
CN 1H-Pyrrole-3-carboxamide, N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L26 ANSWER 45 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:902199 CAPLUS
DOCUMENT NUMBER: 141:374704
TITLE: Composition and uses of galectin antagonists to augment treatment of cancer or other proliferative disorders
INVENTOR(S): Chang, Yan; Sasak, Vodek
PATENT ASSIGNEE(S): Glycogenesys, Inc., USA
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004091634	A1	20041028	WO 2004-US10675		20040407
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004023925	A1	20040205	US 2003-408723		20030407
US 2004223971	A1	20041111	US 2004-819901		20040407
PRIORITY APPLN. INFO.:			US 2003-408723	A	20030407
			US 2003-461006P	P	20030407
			US 2003-474562P	P	20030530
			US 2001-299991P	P	20010621
			US 2002-176235	A2	20020620

AB The present invention is directed to methods and compns. for augmenting treatment of cancers and other proliferative disorders. In particular embodiments, the invention combines the administration of an agent that inhibits the anti-apoptotic activity of galectin-3 (e.g., a 'galectin-3 inhibitor') so as to potentiate the toxicity of a **chemotherapeutic** agent. In certain preferred embodiments, the conjoint therapies of the present invention can be used to improve the efficacy of those **chemotherapeutic** agents whose cytotoxicity is influenced by the status of an anti-apoptotic Bcl-2 protein for the treated cell. For instance, galectin-3 inhibitors can be administered in combination with a **chemotherapeutic** agent that interferes with DNA replication

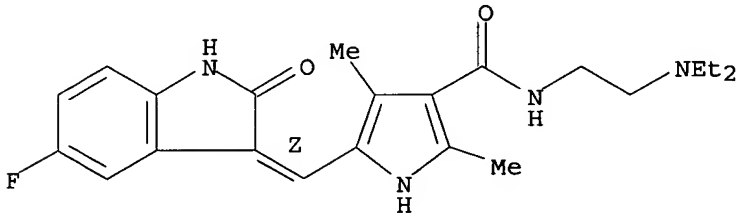
fidelity or cell-cycle progression of cells undergoing unwanted proliferation.

IT **557795-19-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SU 11248; composition and uses of galectin antagonists to augment treatment of cancer or other proliferative disorders)

RN 557795-19-4 CAPLUS

CN 1H-Pyrrole-3-carboxamide, N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

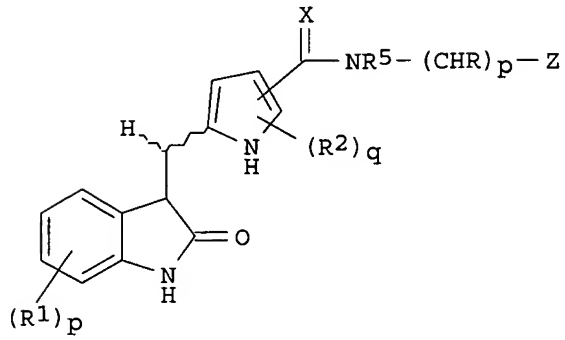
L26 ANSWER 46 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:452964 CAPLUS
DOCUMENT NUMBER: 141:1206
TITLE: Combination administration of an indolinone with a **chemotherapeutic** agent for cell proliferation disorders
INVENTOR(S): Abrams, Tinya; Murray, Lesley; Pryer, Nancy; Cherrington, Julie M.
PATENT ASSIGNEE(S): Sugen, Inc., USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004045523	A2	20040603	WO 2003-US36526	20031114
WO 2004045523	A3	20040930		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
NL 1024779	A1	20040518	NL 2003-1024779	20031114
NL 1024779	C2	20041109		
CA 2506308	AA	20040603	CA 2003-2506308	20031114

US 2004152759	A1	20040805	US 2003-712296		20031114
EP 1562600	A2	20050817	EP 2003-783527		20031114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003015630	A	20050823	BR 2003-15630		20031114
NO 2005002578	A	20050527	NO 2005-2578		20050527
PRIORITY APPLN. INFO.:			US 2002-426386P	P	20021115
			WO 2003-US36526	W	20031114

OTHER SOURCE(S): MARPAT 141:1206

GI



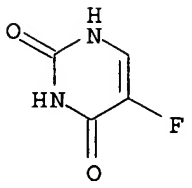
I

AB The invention relates to a method of treating cancer by administering a combination of an indolinone compound with another **chemotherapeutic** agent. The combination of an indolinone compound I (R = H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocycle, amino; R1 = alkyl, halo, alkoxy, etc.; R2 = alkyl, aryl, heteroaryl, etc.; R5 = H, alkyl, aryl, haloalkyl, cycloalkyl, etc.; X = O, S; p = 0, 1, 2, 3; q = 0, 1, 2; Z = OH, -O-alkyl, -NR3R4; R3, R4 = H, alkyl, aryl, heteroaryl, cycloalkyl, heterocycle, or together with N form a ring) with another **chemotherapeutic** agent provides an enhanced effect in treating cancer patients. Mice implanted with MX-1 human breast carcinoma fragments were treated with **docetaxel** and 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide (preparation given).

IT **51-21-8**, **5-Fluorouracil**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as **chemotherapeutic** agent; cancer therapy using combination administration of indolinone compds. with **chemotherapeutic** agents for cell proliferation disorders)

RN 51-21-8 CAPLUS

CN 2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI) (CA INDEX NAME)



L26 ANSWER 47 OF 73 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:100803 CAPLUS
DOCUMENT NUMBER: 140:139483
TITLE: Method for enhancing the effectiveness of therapies of hyperproliferative diseases
INVENTOR(S): Chang, Yan; Sasak, Vodek
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 176,235.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004023925	A1	20040205	US 2003-408723	20030407
US 2003013681	A1	20030116	US 2002-176235	20020620
US 6680306	B2	20040120		
CN 1543351	A	20041103	CN 2002-816003	20020621
US 2004043962	A1	20040304	US 2003-657383	20030908
WO 2004091634	A1	20041028	WO 2004-US10675	20040407

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

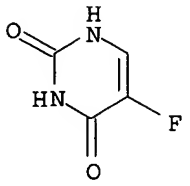
PRIORITY APPLN. INFO.:

US 2001-299991P	P	20010621
US 2002-176235	A2	20020620
US 2003-408723	A	20030407
US 2003-461006P	P	20030407
US 2003-474562P	P	20030530

AB The efficacy of conventional cancer therapies such as surgery, **chemotherapy** and radiation is enhanced by the use of a therapeutic material which binds to and interacts with galectins. The therapeutic material can enhance apoptosis thereby increasing the effectiveness of oncolytic agents. It can also inhibit angiogenesis thereby moderating tumor growth and/or metastasis.

IT **51-21-8, 5-Fluorouracil**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for enhancing effectiveness of therapies of hyperproliferative diseases)

RN 51-21-8 CAPLUS
CN 2,4(1H,3H)-Pyrimidinedione, 5-fluoro- (9CI) (CA INDEX NAME)



L26 ANSWER 48 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004499410 EMBASE
TITLE: Researchers optimistic about targeted drugs for pancreatic cancer.
AUTHOR: McBride G.
SOURCE: Journal of the National Cancer Institute, (3 Nov 2004) Vol. 96, No. 21, pp. 1570-1572.
ISSN: 0027-8874 CODEN: JNCIAM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 014 Radiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
ENTRY DATE: Entered STN: 20041209
Last Updated on STN: 20041209
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 49 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004161776 EMBASE
TITLE: New Systemic Frontline Treatment for Metastatic Colorectal Carcinoma.
AUTHOR: Braun A.H.; Achterrath W.; Wilke H.; Vanhoefer U.; Harstrick A.; Preusser P.
CORPORATE SOURCE: Dr. A.H. Braun, West German Cancer Center, Dept. of Int. Med. (Cancer Research), University of Essen Medical School, Hufelandstr. 55, D-45122 Essen, Germany. adahbraun@yahoo.de
SOURCE: Cancer, (15 Apr 2004) Vol. 100, No. 8, pp. 1558-1577.
Refs: 188
ISSN: 0008-543X CODEN: CANCAR
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040513
Last Updated on STN: 20040513

AB Options for first-line **chemotherapy** in patients with metastatic colorectal carcinoma have broadened considerably with the introduction of **irinotecan** and oxaliplatin. Furthermore, the oral fluoropyrimidine capecitabine has demonstrated efficacy in Phase III

trials and recently was approved for first-line treatment in Europe and the United States. Capecitabine yielded similar median times to disease progression and median survival rates compared with bolus 5-**fluorouracil** (5-FU)/**leucovorin** (LV) (Mayo Clinic/North Central Cancer Treatment Group regimen), with superior and similar response rates, respectively. However, its role as a first-line, single-agent substitute for intermittent infusional 5-FU/LV remains to be defined. The addition of **irinotecan** or oxaliplatin to 5-FU/LV resulted in improved response rates and progression-free survival in large, randomized trials; moreover, **irinotecan**-containing regimens resulted in improved overall survival. Prevalent regimens of **irinotecan**/5-FU/LV and oxaliplatin/5-FU/LV have been compared in two randomized Phase III trials. One study demonstrated the statistical superiority of oxaliplatin/infusional 5-FU/LV over **irinotecan** /bolus 5-FU/LV in terms of response, time to disease progression, and median survival; however, those advantages may have been attributable to infusional administration or to major differences in second-line therapy. A randomized Phase III study comparing **irinotecan** and oxaliplatin in combination with the same infusional 5-FU/LV regimens and crossover in case of disease progression showed equivalent efficacy for both schedules in the first-line setting, but the **irinotecan** combination proved beneficial in terms of safety. New molecular targeted agents, such as angiogenesis-modulating compounds (e.g., bevacizumab) and epidermal growth factor receptor inhibitors (e.g., cetuximab), are under clinical investigation. This review updates current systemic frontline treatments and future perspectives for patients with advanced colorectal carcinoma. .COPYRGT. 2004 American Cancer Society.

L26 ANSWER 50 OF 73 EMBASE

ACCESSION NUMBER: 2004531655 EMBASE
TITLE: Development of TGF-β signalling inhibitors for cancer therapy.
AUTHOR: Yingling J.M.; Blanchard K.L.; Sawyer J.S.
CORPORATE SOURCE: J.M. Yingling, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, United States. yingling_jonathan_m@lilly.com
SOURCE: Nature Reviews Drug Discovery, (2004) Vol. 3, No. 12, pp. 1011-1022.
Refs: 118
ISSN: 1474-1776 CODEN: NRDDAG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041230
Last Updated on STN: 20041230

AB The transforming growth factor-β (TGF-β) superfamily of ligands has a pivotal role in the regulation of a wide variety of physiological processes from development to pathogenesis. Since the discovery of the prototypic member, TGF-β, almost 20 years ago, there have been tremendous advances in our understanding of the complex biology of this superfamily. Deregulation of TGF-β has been implicated in the pathogenesis of a variety of diseases, including cancer and fibrosis. Here we present the rationale for evaluating TGF-β signalling inhibitors as cancer therapeutics, the structures of small-molecule

inhibitors that are in development and the targeted drug discovery model that is being applied to their development.

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ACCESSION NUMBER: 2004406308 EMBASE
TITLE: [40 Years quality in oncology. The Annual Meeting of the American Society of Clinical Oncology 2004].
40 JAHRE QUALITAT IN DER ONKOLOGIE. JAHRESTAGUNG DER AMERICAN SOCIETY OF CLINICAL ONCOLOGY 2004.
AUTHOR: Junker A.
CORPORATE SOURCE: A. Junker, Apothekerin fur Klin./Onkol. Pharm., Sana Klinikum Remscheid GmbH, Burger Strasse 211, 42859 Remscheid, Germany
SOURCE: Krankenhauspharmazie, (2004) Vol. 25, No. 9, pp. 417-421.
Refs: 16
ISSN: 0173-7597 CODEN: KRANDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 006 Internal Medicine
016 Cancer
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: German
SUMMARY LANGUAGE: German
ENTRY DATE: Entered STN: 20041007
Last Updated on STN: 20041007
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 52 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004424352 EMBASE
TITLE: [Targeted treatments by ASCO 2004 - Biology/pharmacodynamics transversal: Clinical pharmacology in phase I].
TRAITEMENTS CIBLES A L'ASCO 2004 - TRANSVERSALE BIOLOGIE/PHARMACODYNAMIQUE: PHARMACOLOGIE CLINIQUE DE PHASE I.
AUTHOR: Spano J.-P.; Raymond E.
CORPORATE SOURCE: J.-P. Spano, Hopital Pitie-Salpetriere, Serv. d'Oncologie Med. du Pr Khayat, 47-63, bd de l'Hopital, F-75013 Paris, France
SOURCE: Oncologie, (2004) Vol. 6, No. 5, pp. 373-375.
ISSN: 1292-3818 CODEN: OOLOFG
COUNTRY: France
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: French
ENTRY DATE: Entered STN: 20041028
Last Updated on STN: 20041028
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 53 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004424350 EMBASE
TITLE: [Targeted treatments by ASCO 2004 - Introduction].
TRAITEMENTS CIBLES A L'ASCO 2004 - INTRODUCTION.

AUTHOR: Milano G.
CORPORATE SOURCE: G. Milano, Centre Antoine-Lacassagne, 33, avenue de Valombrose, F-06189 Nice Cedex 2, France
SOURCE: Oncologie, (2004) Vol. 6, No. 5, pp. 369.
ISSN: 1292-3818 CODEN: OOLOFG
COUNTRY: France
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: French
ENTRY DATE: Entered STN: 20041028
Last Updated on STN: 20041028
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 54 OF 73 EMBASE
ACCESSION NUMBER: 2004480069 EMBASE
TITLE: Vascular remodeling and clinical resistance to antiangiogenic cancer therapy.
AUTHOR: Glade Bender J.; Cooney E.M.; Kandel J.J.; Yamashiro D.J.
CORPORATE SOURCE: dy39@columbia.edu
SOURCE: Drug Resistance Updates, (2004) Vol. 7, No. 4-5, pp. 289-300.
Refs: 101
ISSN: 1368-7646 CODEN: DRUPFW
PUBLISHER IDENT.: S 1368-7646(04)00068-8
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041202
Last Updated on STN: 20041202
AB When first conceived, antiangiogenic therapy for cancer offered the possibility of universal efficacy, low toxicity, and little possibility of resistance. Blockade of the vascular endothelial growth factor (VEGF) pathway has yielded the most promising results both in animal models and in patients. However, resistance to VEGF blockade has been found even when given in combination with **chemotherapy** or other antiangiogenic agents. This resistance is associated with remodeled vasculature and with increased expression of angiogenic factors, such as PDGF-B and angiopoietin-1, which may contribute to vessel stabilization. Future efforts must be directed towards the identification of factors associated with vascular remodeling in order to improve the efficacy of antiangiogenic therapy. .COPYRGT. 2004 Elsevier Ltd. All rights reserved.

L26 ANSWER 55 OF 73 EMBASE
ACCESSION NUMBER: 2004362334 EMBASE
TITLE: Targeted therapy in non-small cell lung cancer.
AUTHOR: Shou-Ching T.
CORPORATE SOURCE: stang@med.miami.edu
SOURCE: Chinese Journal of Lung Cancer, (2004) Vol. 7, No. 4, pp. 284-289.
Refs: 38
ISSN: 1009-3419 CODEN: ZFZHAG
COUNTRY: China

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20040916
Last Updated on STN: 20040916
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 56 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004285013 EMBASE
TITLE: Therapeutically targeted anticancer agents: Inhibitors of receptor tyrosine kinases.
AUTHOR: Garcia-Echeverria C.; Fabbro D.
CORPORATE SOURCE: C. Garcia-Echeverria, Oncology Research, Novartis Pharma AG, CH-4002 Basel, Switzerland. carlos.garcia-echeverria@pharma.novartis.com
SOURCE: Mini-Reviews in Medicinal Chemistry, (2004) Vol. 4, No. 3, pp. 273-283.
Refs: 168
ISSN: 1389-5575 CODEN: MMCIAE
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040722
Last Updated on STN: 20040722
AB The rationale to target receptor protein tyrosine kinases (RPTKs) as an approach to cancer **chemotherapy** has continued to become more compelling with time. Preclinical and clinical data strongly support the involvement of specific RPTKs in the formation and progression of a subset of solid and liquid tumors. The advances in our understanding of the oncogenic activation of these receptors have been matched by the identification of new structural classes of kinase inhibitors that exhibit enormous improvements with regard to potency, specificity and efficacy. This article summarizes current knowledge of the most promising RPTK inhibitors in clinical trials or known to be in late stage preclinical development. .COPYRGT. 2004 Bentham Science Publishers Ltd.

L26 ANSWER 57 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004165530 EMBASE
TITLE: Role of **chemotherapy** in patients with soft tissue sarcomas.
AUTHOR: Maki R.G.
CORPORATE SOURCE: Dr. R.G. Maki, Department of Medicine, Memorial Sloan-Kettering Cancer Ctr., 1275 York Avenue, New York, NY 10021, United States. makir@mskcc.org
SOURCE: Expert Review of Anticancer Therapy, (2004) Vol. 4, No. 2, pp. 229-236.
Refs: 36

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

ISSN: 1473-7140 CODEN: ERATBJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040429
Last Updated on STN: 20040429

AB The management of soft tissue sarcomas has been highlighted in the last few years by the responsiveness of gastrointestinal stromal tumors to imatinib (Gleevec®, Novartis). In this article, the use of **chemotherapeutic** agents in the management of this and some of the 50 or more subtypes of sarcomas are discussed, and a brief review of the use of **chemotherapy** in the adjuvant or neoadjuvant setting for people with large extremity sarcomas is provided. **Doxorubicin** and ifosfamide (Mitoxona®, Bristol-Myers Squibb) remain the best individual drugs for sarcomas overall, although dacarbazine and gemcitabine (Gemzar®, Eli Lilly) with or without a taxane has activity in at least a subset of sarcomas. The data regarding adjuvant **chemotherapy** for extremity soft tissue sarcomas is still quite mixed, with little if any overall survival advantage found to support its incorporation into disease management. The finding of tyrosine kinase inhibitors such as imatinib with demonstrated activity in gastrointestinal stromal tumors and dermatofibrosarcoma protuberans, as well as the finding of new agents such as ecteinascidin-743 (Yondelis®, PharmaMar) with at least some activity against soft tissue sarcomas, reinforces the idea that we should target individual subtypes of sarcoma, just as treatment varies by subtype for the hematological malignancies. .COPYRGT. Future Drugs Ltd. All rights reserved.

ACCESSION NUMBER: 2004525777 EMBASE
TITLE: Vascular endothelial growth factor antagonists as anticancer agents.
AUTHOR: Hasan J.; Jayson G.C.
CORPORATE SOURCE: Dr. J. Hasan, Department of Medical Oncology, Christie Hospital, Wilmslow Road, Manchester, M20 4BX, United Kingdom. Jurgees.Hasan@christie-tr.nwest.nhs.uk
SOURCE: American Journal of Cancer, (2004) Vol. 3, No. 4, pp. 229-245.
Refs: 207
ISSN: 1175-6357 CODEN: AJCMCB
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041230
Last Updated on STN: 20041230

AB The most potent angiogenic cytokine is vascular endothelial growth factor (VEGF). A number of strategies have been developed to inhibit the

activity of the VEGF molecule and its receptors. These strategies include gene therapy techniques that deliver antisense oligonucleotides, soluble VEGF receptors that function in a dominant negative fashion, and ribozymes. Recombinant monoclonal anti-VEGF antibodies such as bevacizumab and tyrosine kinase (TK) receptor inhibitors directed against the VEGF receptors appear to be the most promising. These agents have demonstrated broad-spectrum antitumor activity in early clinical trials in a wide range of human solid tumors and hematological malignancies. The TK receptor inhibitors are of particular interest as they can be administered orally. Early trials have reported vascular toxicities, including hemorrhagic and thromboembolic events. However, myelotoxicity is rarely seen, which enables these agents to be administered in combination with cytotoxic agents. Studies of **chemotherapy** and VEGF inhibitors are underway but the benefits of these regimens will need to be established in adequately powered phase III studies. Theoretically, these agents, are likely to be most effective in diseases with a low tumor burden, for example, when administered as adjuvant therapy in early cancer and as maintenance therapy in advanced cancers. Other potential indications include the treatment of premalignant conditions. However, the overall development of these agents can only be optimized if appropriate biologic endpoints are identified and incorporated into clinical trials.

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ACCESSION NUMBER: 2004438026 EMBASE
TITLE: Novel therapies for pancreatic adenocarcinoma.
AUTHOR: Pino S.M.; Xiong H.Q.; McConkey D.; Abbruzzese J.L.
CORPORATE SOURCE: Dr. S.M. Pino, Dept. of Gastrointest. Med. Oncology, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, United States
SOURCE: Current Oncology Reports, (2004) Vol. 6, No. 3, pp. 199-206.
Refs: 50
ISSN: 1523-3790 CODEN: CORUAT
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20041028
Last Updated on STN: 20041028

AB Despite advances in our understanding of the molecular and genetic basis of pancreatic cancer, the disease remains a clinical challenge. Gemcitabine, the standard **chemotherapy** for pancreatic cancer, offers modest improvement of tumor-related symptoms and marginal advantage of survival. New approaches, alone and in combination with gemcitabine, are being developed to combat this cancer. In this article we review the current status of investigations into several classes of agents: matrix metalloproteinase inhibitors; farnesyl transferase inhibitors; epidermal growth factor receptor inhibitors, including monoclonal antibodies and tyrosine kinase inhibitors; cyclooxygenase-2 inhibitors, and others. The scientific rationale, mechanism of action, and clinical trial data for these novel agents are discussed. Copyright .COPYRGT. 2004 by Current Science Inc.

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ACCESSION NUMBER: 2005014849 EMBASE
TITLE: Angiogenesis-targeted therapies in prostate cancer.
AUTHOR: Lara Jr. P.N.; Twardowski P.; Quinn D.I.
CORPORATE SOURCE: Dr. P.N. Lara Jr., University of California, Davis Cancer Center, 4501 X St, Sacramento, CA 95817, United States. primo.lara@ucdmc.ucdavis.edu
SOURCE: Clinical Prostate Cancer, (2004) Vol. 3, No. 3, pp. 165-173.
Refs: 147
ISSN: 1540-0352 CODEN: CPCLC4
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050120
Last Updated on STN: 20050120

AB Most patients with metastatic prostate cancer will respond initially to ablation of gonadal androgen production. Eventually, all patients will develop progressive disease despite continued androgen suppression, a condition called androgen-independent or hormone-refractory prostate cancer. Hormone-refractory prostate cancer is characterized by virulent biologic and clinical behavior. Recently, **docetaxel**-based **chemotherapy** has been shown to improve survival and quality of life in this disease when compared with mitoxantrone-based therapy. However, results remain suboptimal. Recently, there have been remarkable advances in the delineation of the mechanisms of cancer growth, metastasis, and the intricate interactions between tumor cells and the surrounding normal tissues. The accumulated evidence has confirmed the importance of angiogenesis in these processes and validated the theory that inhibition of neovascularization is a promising therapeutic anticancer strategy. Currently, dozens of compounds that interfere with different steps of the angiogenic cascade are in preclinical and clinical development. Some of these agents have exhibited promising antitumor activity in hormone-refractory prostate cancer. This review summarizes the molecular mechanisms implicating angiogenesis in the development and progression of advanced-stage prostate cancer, as well as the drug development efforts that are targeting this process.

L26 ANSWER 61 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004350097 EMBASE
TITLE: Vascular endothelial growth factor in esophageal cancer.
AUTHOR: Kleespies A.; Guba M.; Jauch K.-W.; Bruns C.J.
CORPORATE SOURCE: Dr. A. Kleespies, Department of Surgery, Klinikum Grosshadern, Ludwig-Maximilian-University, Marchioninistrasse 15, 81377 Munich, Germany. axelkleespies@aol.com
SOURCE: Journal of Surgical Oncology, (1 Aug 2004) Vol. 87, No. 2, pp. 95-104.
Refs: 92
ISSN: 0022-4790 CODEN: JSONAU
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy

011 Otorhinolaryngology
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040902
Last Updated on STN: 20040902

AB Vascular endothelial growth factor (VEGF) plays a crucial role in angiogenesis of many solid malignancies. The influence of angiogenesis and VEGF expression on progression and recurrence of esophageal cancer has been investigated over the last years. This article reviews the prognostic significance of VEGF expression, microvessel density (MVD), and lymphangiogenic factors in squamous cell carcinoma (SCC), Barrett's dysplasia, and adenocarcinoma (AC) of the esophagus, their predictive value for treatment response to chemo-radiotherapy and new anti-angiogenic treatment strategies. .COPYRGT. 2004 Wiley-Liss, Inc.

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ACCESSION NUMBER: 2004245740 EMBASE
TITLE: New cancer therapeutics: Target-specific in, cytotoxics out?.
AUTHOR: Broxterman H.J.; Georgopapadakou N.H.
CORPORATE SOURCE: H.J. Broxterman, Department of Medical Oncology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands. h.broxterman@vumc.nl
SOURCE: Drug Resistance Updates, (2004) Vol. 7, No. 2, pp. 79-87.
Refs: 59
ISSN: 1368-7646 CODEN: DRUPFW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040628
Last Updated on STN: 20040628

AB The International Conference on Molecular Targets and Therapeutics, jointly sponsored by the American Association for Cancer Research (AACR), National Cancer Institute (NCI) and European Organization for Research and Treatment of Cancer (EORTC), was held in Boston on November 17-21, 2003. It offered updates of the latest developments and emerging trends in anti-cancer research. One of the most exciting areas was the development of molecular target-specific therapeutics that have the potential to maximize therapeutic benefit while minimizing toxicity to normal cells. Signifying the coming of age of tumour-specific targets and agents was the recurring theme, to urgently develop and validate biomarker assays as surrogate endpoints; both for showing that targeted agents act as expected and for providing proof of concept in the scientific rationale of new agents. Given the dominance of protein tyrosine kinase inhibitors in small-molecule drug design, a strong case was made for the implementation of phospho-proteomics or signal transduction signatures and pharmaco-proteomics or **chemotherapeutic** scans in phase I/II trials-or for the future "Nanolab", eloquently described by Leroy Hood. However, molecular targeted agents-other than imanitib (Gleevec)-have yet to enter broad clinical use and several presentations described efforts for improving classical (cytotoxic) **chemotherapeutic** agents by targeting them selectively to tumour cells. .COPYRGT. 2004 Elsevier Ltd.

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ACCESSION NUMBER: 2004077253 EMBASE
TITLE: [Controversies and innovations in the treatment of gastrointestinal tumors. Interdisciplinary symposium, Essen, Germany, 26-27 September 2003]. KONTROVERSEN UND INNOVATIONEN IN DER THERAPIE GASTROINTESTINALER TUMOREN. INTERDISZIPLINARES SYMPOSIUM, ESSEN, 26.-27.09.2003.
AUTHOR: Mono M.L.; Junker A.
CORPORATE SOURCE: M.L. Mono, Fruhlingstrasse 38, 45133 Essen, Germany. malumono@gmx.de
SOURCE: Onkologe, (2004) Vol. 10, No. 1, pp. 77-81.
Refs: 9
ISSN: 0947-8965 CODEN: ONKOF4
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: German
ENTRY DATE: Entered STN: 20040304
Last Updated on STN: 20040304
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L26 ANSWER 64 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005019219 EMBASE
TITLE: Vascular Endothelial Growth Factor (VEGF) inhibition by small molecules.
AUTHOR: Ahmed S.I.; Thomas A.L.; Steward W.P.
CORPORATE SOURCE: Prof. W.P. Steward, Clinical Oncology, Osborne Building, Leicester Royal Infirmary, Leicester, LE1 5WW, United Kingdom. wps1@leicester.ac.uk
SOURCE: Journal of Chemotherapy, (2004) Vol. 16, No. SUPPL. 4, pp. 59-63.
Refs: 18
ISSN: 1120-009X CODEN: JCHEEU
COUNTRY: Italy
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050127
Last Updated on STN: 20050127

AB Angiogenesis is essential for primary tumours to grow and metastasise, and is driven by the production of positive angiogenic factors. The Vascular Endothelial Growth Factor (VEGF) family is central to the process of angiogenesis and comprises 5 molecules designated A, B, C, D and E. VEGF is overexpressed in several solid malignancies. The actions of VEGF are mediated through receptors possessing tyrosine kinase activity: VEGFH-1 (Flt-1), VEGFR-2 (Kdr/Flk-1) and VEGFH-3 (Flt-4). Anti-VEGF strategies include the use of antibodies to VEGF or its receptors, the use of ribozymes to decrease receptor expression, and the use of inhibitors of

tyrosine kinase to reduce receptor activation and downstream signalling. The focus of this review is small molecule inhibitors of VEGF receptors which target their intrinsic tyrosine kinase activity. The clinical development of the following agents is discussed: SU5416, SU11248, SU6668, PTK/ZK, ZD6474.

L26 ANSWER 65 OF 73 EMBASE

ACCESSION NUMBER: 2004078742 EMBASE
TITLE: New anticancer agents and therapeutic strategies in development for solid cancers: A clinical perspective.
AUTHOR: Awada A.; Mano M.; Hendlisz A.; Piccart M.
CORPORATE SOURCE: A. Awada, Chemotherapy Unit, Jules Bordet Institute, Rue Heger-Bordet 1, B-1000 Brussels, Belgium. ahmad.awada@bordet.be
SOURCE: Expert Review of Anticancer Therapy, (2004) Vol. 4, No. 1, pp. 53-60.
Refs: 20
ISSN: 1473-7140 CODEN: ERATBJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040304
Last Updated on STN: 20040304

AB In addition to well-known **chemotherapeutic** agents used in the treatment of solid cancers, promising novel cytotoxic agents are being investigated. Among them are analogs of existing cytotoxic agents, aimed at improving the therapeutic index, and new families such as the epothilone compounds. Agents that target the tyrosine kinase-dependent pathways, farnesyl transferase modulators, Raf kinase inhibitors, antisense molecules to Bcl-2 and proteasome modulators, agents that bind to key proteins involved in critical phases of the cell cycle, as well as antiangiogenesis strategies, are all promising approaches in the treatment of solid cancers. The combination of cytotoxics, hormonal agents or radiotherapy with new molecular-targeted therapies represents one of the main strategies to improve survival in solid cancers. A clinical perspective of these agents as monotherapy or combination therapy will be presented in this paper.

L26 ANSWER 66 OF 73 EMBASE

ACCESSION NUMBER: 2004026575 EMBASE
TITLE: Resistance to anti-VEGF agents.
AUTHOR: Ton N.C.; Jayson G.C.
CORPORATE SOURCE: N.C. Ton, Cancer Research UK Dept. Med. Oncol., Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 4BX, United Kingdom. Nton@picr.man.ac.uk
SOURCE: Current Pharmaceutical Design, (2004) Vol. 10, No. 1, pp. 51-64.
Refs: 148
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology

037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040129
Last Updated on STN: 20040129

AB The number of anti-angiogenic agents developed for clinical use has risen greatly over the past decade. Currently, more than 80 are in trials ranging from phase I through to phase III studies and many more are in preclinical evaluation. Much hope was envisaged for these new agents to become the panacea of anti-tumoural treatment. Unfortunately the single agent activity to date has proven to be disappointing although one trial has recently reported a survival advantage when **chemotherapy** was administered with anti-VEGF antibodies in the setting of advanced colorectal cancer. To an extent, this may be due to great expectations of cytostatic compounds, but recently many factors have been examined to explain the differences between clinical and experimental findings. In this review, some of the factors responsible for the discrepancy are examined, with a specific focus on inhibitors of VEGF. The key factors responsible for the lack of activity are tumour heterogeneity and redundancy in the VEGF signalling system. An increased understanding of these factors is critical to the development of effective anti-angiogenic agents and need to be taken into account as new generations of drugs emerge.

L26 ANSWER 67 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005019214 EMBASE
TITLE: Strategies for multiple signalling inhibition.
AUTHOR: Tortora G.; Bianco R.; Daniele G.
CORPORATE SOURCE: G. Tortora, Via Pansini 5, 80131 Napoli, Italy. tortora@unina.it
SOURCE: Journal of Chemotherapy, (2004) Vol. 16, No. SUPPL. 4, pp. 41-43.
Refs: 10
ISSN: 1120-009X CODEN: JCHEEU
COUNTRY: Italy
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050127
Last Updated on STN: 20050127

AB Cancer cells hyperactivate signalling molecules, including EGFR, Akt and the angiogenic factor VEGF to escape apoptosis, thus contributing also to resistance to treatment. While single signalling inhibitors have produced limited advantages in clinical trials, their combination with conventional treatments is more effective; however, the rate of responses is generally around 20%. A major limitation is represented by the activation of escape pathways, due to an intensive cross-talk and redundancy of signals in the transduction network. A novel and more rational approach is the combination of multiple signalling inhibitors, according to the molecular context of disease, in combination with selected conventional treatments.

L26 ANSWER 68 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005064141 EMBASE
TITLE: Future directions in the use of antiangiogenic agents in

patients with colorectal cancer.
AUTHOR: Hoff P.M.
CORPORATE SOURCE: Dr. P.M. Hoff, Dept. of Gastrointest. Med. Oncology, University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030-4009. phoff@madanderson.org
SOURCE: Seminars in Oncology, (2004) Vol. 31, No. SUPPL. 17, pp. 17-21.
Refs: 30
ISSN: 0093-7754 CODEN: SOLGAV
PUBLISHER IDENT.: S 0093-7754(04)00594-9
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050218
Last Updated on STN: 20050218

AB Considerable progress has been achieved in the treatment of colorectal cancer over the last few years, but it remains a major cause of cancer death in the United States. Among the most important recent developments is the understanding that angiogenesis is a fundamental requirement of early tumor growth and metastasis and therefore is an important target for therapy. The recent positive results obtained by adding bevacizumab to a standard regimen of **chemotherapy** highlight the potential impact of angiogenesis. Although not the final answer to the problem of advanced colorectal cancer, the success obtained with bevacizumab should encourage the development of even more effective and less toxic molecular targeted agents and regimens. The tyrosine kinase inhibitor vatalanib (PTK787/ZK222584) is in the final stages of clinical development, and several other promising compounds will be available for clinical development in the near future. Agents already commercially available, such as the monoclonal antibody cetuximab, may have some antiangiogenic properties as well. However, the greatest benefit from antiangiogenic therapies may come from their combined use, not only with conventional **chemotherapy** but also with other molecular targeted agents, radiotherapy, and surgery in a true multidisciplinary approach. .COPYRGT. 2004 Elsevier Inc. All rights reserved.

L26 ANSWER 69 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004206734 EMBASE
TITLE: Update on the Management of Connective Tissue Malignancies.
AUTHOR: Fanucchi M.
CORPORATE SOURCE: Dr. M. Fanucchi, Winship Cancer Institute, Emory University, Bldg. C, 1365 Clifton Rd, Atlanta, GA 30322, United States
SOURCE: Seminars in Oncology, (2004) Vol. 31, No. 2 SUPPL. 4, pp. 16-19.
Refs: 27
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 006 Internal Medicine
016 Cancer
037 Drug Literature Index

048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040604
Last Updated on STN: 20040604

AB Approximately 11,000 new cases of connective tissue malignancies are anticipated in 2004. These diseases can be divided into soft-tissue sarcomas, sarcomas of bone, and gastrointestinal stromal tumors. Optimal management of these diseases requires a multidisciplinary team with expertise in surgery, pathology, radiotherapy, and **chemotherapy.** Over half of patients with stage III soft tissue and bone sarcomas are cured, as are some patients with metastatic disease. Imatinib mesylate has been an important advance in the treatment of gastrointestinal stromal tumors.

L26 ANSWER 70 OF 73 EMBASE
ACCESSION NUMBER: 2005064140 EMBASE
TITLE: Angiogenesis inhibitors in the treatment of colorectal cancer.
AUTHOR: Iqbal S.; Lenz H.-J.
CORPORATE SOURCE: Dr. H.-J. Lenz, University of Southern California, Norris Comprehensive Cancer Center, 1441 Eastlake Ave, Los Angeles, CA 90033. lenz@usc.edu
SOURCE: Seminars in Oncology, (2004) Vol. 31, No. SUPPL. 17, pp. 10-16.
Refs: 38
ISSN: 0093-7754 CODEN: SOLGAV
PUBLISHER IDENT.: S 0093-7754(04)00593-7
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050218
Last Updated on STN: 20050218

AB Angiogenesis is critical for normal and pathologic processes in new blood vessel formation. A recent significant advance in the treatment of metastatic colorectal cancer has occurred by the development of agents targeting key regulatory molecules involved in this process, specifically vascular endothelial growth factor (VEGF). These angiogenesis inhibitors, include bevacizumab (Avastin, Genentech, Inc, South San Francisco, CA), which binds free VEGF. Recently, a phase III, multicenter, double-blind, randomized, placebo-controlled trial was designed to determine whether or not the addition of bevacizumab to first-line **irinotecan**, **5-fluorouracil**, and **leucovorin** **chemotherapy** was completed in patients with metastatic colorectal cancer. The trial showed a higher response rate, longer time to tumor progression, and prolonged overall survival in patients with metastatic colorectal cancer. Of note, this was the first large, randomized, phase III study to show the importance of targeting VEGF and tumor angiogenesis for the treatment of human cancer. Other potential targets of angiogenesis, such as the VEGF receptor and multi-targeted agents, are undergoing evaluation in clinical trials.

L26 ANSWER 71 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004063661 EMBASE
TITLE: Angiogenesis inhibitors in clinical development; where are we now and where are we going?.
AUTHOR: Eskens F.A.L.M.
CORPORATE SOURCE: Dr. F.A.L.M. Eskens, Department of Medical Oncology, Erasmus University Medical Center, PO Box 2040, Rotterdam 3000 CA, Netherlands. f.eskens@erasmusmc.nl
SOURCE: British Journal of Cancer, (12 Jan 2004) Vol. 90, No. 1, pp. 1-7.
Refs: 62
ISSN: 0007-0920 CODEN: BJCAAI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040304
Last Updated on STN: 20040304

AB Angiogenesis is crucial for tumour growth and the formation of metastases. Various classes of angiogenesis inhibitors that are each able to inhibit one of the various steps of this complex process can be distinguished. Results from clinical studies with these agents are summarised. In general, it has been shown that most angiogenesis inhibitors can be safely administered, but that tumour regressions are rare. Combining angiogenesis inhibitors with cytotoxic **chemotherapy** can enhance anticancer activity. Recently, some promising data with regard to clinical efficacy have been presented. While performing clinical studies with angiogenesis inhibitors, defining biological activity is crucial, but thus far no validated techniques are available. It is conceivable that in the near future various classes of angiogenesis inhibitors will be combined in an attempt to further improve antiangiogenic and anticancer activity. .COPYRGT. 2004 Cancer Research UK.

L26 ANSWER 72 OF 73 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004301745 EMBASE
TITLE: [Designer-drugs in tumor treatment].
DESIGNERMEDIKAMENTE IN DER TUMORTHERAPIE.
AUTHOR: Beck C.; Kneba M.
CORPORATE SOURCE: Dr. M. Kneba, II. Medizinishe Klin. und Poliklinik, Univ.-Klinikum Schleswig-Holstein, Campus Kiel, Chemnitzstrasse 33, 24116 Kiel, Germany. sekretariat@med2.uni-kiel.de
SOURCE: Internist, (2004) Vol. 45, No. SUPPL. 1, pp. S38-S47.
Refs: 71
ISSN: 0020-9554 CODEN: INTEAG
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: German
SUMMARY LANGUAGE: English; German
ENTRY DATE: Entered STN: 20040805

Last Updated on STN: 20040805

AB Targeted approaches to treat malignant diseases in hematology and oncology based on the molecular basis of the disease represent a major breakthrough in modern medicine. Knowledge acquired in basic sciences such as functional understanding of products generated by chromosomal translocations, definition of surface molecules or molecular requirements of tumor-cell survival allow to specifically aim at the cause of or at a requirement for malignancy. This is in sharp contrast to conventional **chemotherapy** which mainly influences the ubiquitous pathways of nucleic acid metabolism and cell division. In addition to superior efficacy of these approaches one should - on the long run - expect a superior profile of side effects compared to standard regimens. These "designer-approaches" are mainly based on small molecules or monoclonal antibodies. Out of the broad spectrum of current concepts we would like to summarize some of the strategies that have already found their way from bench to bedside.

L26 ANSWER 73 OF 73 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 3

ACCESSION NUMBER: 2003:310928 BIOSIS
DOCUMENT NUMBER: PREV200300310928
TITLE: SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer.
AUTHOR(S): Abrams, Tinya J. [Reprint Author]; Lee, Leslie B.; Murray, Lesley J.; Pryer, Nancy K.; Cherrington, Julie M.
CORPORATE SOURCE: Preclinical Research and Exploratory Development, SUGEN, Inc., 230 East Grand Avenue, South San Francisco, CA, 94080, USA
tinya-abrams@sugen.com
SOURCE: Molecular Cancer Therapeutics, (May 2003) Vol. 2, No. 5, pp. 471-478. print.
ISSN: 1535-7163 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 2003
Last Updated on STN: 2 Jul 2003

AB The purpose of this study was to evaluate the activity of the indolinone kinase inhibitor SU11248 against the receptor tyrosine kinase KIT in vitro and in vivo, examine the role of KIT in small cell lung cancer (SCLC), and anticipate clinical utility of SU11248 in SCLC. SU11248 is an oral, multitargeted tyrosine kinase inhibitor with direct antitumor and antiangiogenic activity through targeting platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor, KIT, and FLT3 receptors. Treatment of the KIT-expressing SCLC-derived NCI-H526 cell line in vitro with SU11248 resulted in dose-dependent inhibition of stem cell factor-stimulated KIT phosphotyrosine levels and proliferation. The biological significance of KIT inhibition was evaluated in vivo by treating mice bearing s.c. NCI-H526 tumors with SU11248 or another structurally unrelated KIT inhibitor, STI571 (Gleevec), which is also known to inhibit Bcr-Abl and PDGFRbeta. SU11248 treatment resulted in significant tumor growth inhibition, whereas inhibition from STI571 treatment was less dramatic. Both compounds reduced phospho-KIT levels in NCI-H526 tumors, with a greater reduction by SU11248, correlating with efficacy. Likewise, phospho-PDGFRbeta levels contributed by tumor stroma and with known involvement in angiogenesis were strongly inhibited by SU11248 and less so by STI571. Because platinum-based **chemotherapy** is part of the standard of care for SCLC, SU11248 was combined with **cisplatin**, and significant tumor growth delay was measured compared with either agent alone. These results expand the

profile of SU11248 as a KIT signaling inhibitor and suggest that SU11248 may have clinical potential in the treatment of SCLC via direct antitumor activity mediated via KIT as well as tumor angiogenesis via vascular endothelial growth factor receptor FLK1/KDR and PDGFRbeta.

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L27          56 FILE MEDLINE
L28         111 FILE BIOSIS
L29          50 FILE EMBASE
L30          44 FILE CAPLUS

TOTAL FOR ALL FILES
L31         261 ABRAMS T?/AU


L32         695 FILE MEDLINE
L33         848 FILE BIOSIS
L34         560 FILE EMBASE
L35         376 FILE CAPLUS

TOTAL FOR ALL FILES
L36        2479 MURRAY L?/AU


L37          16 FILE MEDLINE
L38          31 FILE BIOSIS
L39          12 FILE EMBASE
L40          18 FILE CAPLUS

TOTAL FOR ALL FILES
L41          77 PRYER N?/AU OR DRYER N?/AU

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L43           5 FILE BIOSIS
L44           1 FILE EMBASE
L45           4 FILE CAPLUS

TOTAL FOR ALL FILES
L46          13 L31 AND L36 AND L41

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=> d 1-6 ibib abs;s cancer or neoplasm or tumour or tumor or melanoma

L47  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:452964  CAPLUS
DOCUMENT NUMBER:          141:1206
TITLE:                    Combination administration of an indolinone with a
                          chemotherapeutic agent for cell proliferation
                          disorders
INVENTOR(S):              Abrams, Tinya; Murray, Lesley;
                          Pryer, Nancy; Cherrington, Julie M.
PATENT ASSIGNEE(S):       Sugen, Inc., USA
SOURCE:                   PCT Int. Appl., 87 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
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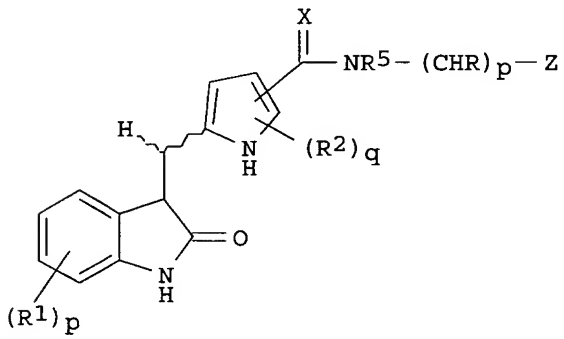
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004045523	A2	20040603	WO 2003-US36526	20031114
WO 2004045523	A3	20040930		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
NL 1024779	A1	20040518	NL 2003-1024779	20031114
NL 1024779	C2	20041109		
CA 2506308	AA	20040603	CA 2003-2506308	20031114
US 2004152759	A1	20040805	US 2003-712296	20031114
EP 1562600	A2	20050817	EP 2003-783527	20031114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003015630	A	20050823	BR 2003-15630	20031114
NO 2005002578	A	20050527	NO 2005-2578	20050527
PRIORITY APPLN. INFO.:			US 2002-426386P P	20021115
			WO 2003-US36526 W	20031114

OTHER SOURCE(S): MARPAT 141:1206
GI



I

AB The invention relates to a method of treating cancer by administering a combination of an indolinone compound with another chemotherapeutic agent. The combination of an indolinone compound I (R = H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocycle, amino; R1 = alkyl, halo, alkoxy, etc.; R2 = alkyl, aryl, heteroaryl, etc.; R5 = H, alkyl, aryl, haloalkyl, cycloalkyl, etc.; X = O, S; p = 0, 1, 2, 3; q = 0, 1, 2; Z = OH, -O-alkyl, -NR3R4; R3, R4 = H, alkyl, aryl, heteroaryl, cycloalkyl, heterocycle, or together with N form a ring) with another chemotherapeutic agent provides an enhanced effect in treating cancer patients. Mice implanted with MX-1 human breast carcinoma fragments were treated with docetaxel and 5-(5-fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide (preparation

given).

L47 ANSWER 2 OF 6 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003501642 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14578466
TITLE: Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with "standard of care" therapeutic agents for the treatment of breast cancer.
AUTHOR: **Abrams Tinya J**; **Murray Lesley J**; Pesenti Enrico; Holway Vicky Walker; Colombo Tina; Lee Leslie B; Cherrington Julie M; **Pryer Nancy K**
CORPORATE SOURCE: Preclinical Research and Experimental Development, SUGEN, Inc., South San Francisco, CA 94080, USA.. tinya-abrams@sugen.com
SOURCE: Molecular cancer therapeutics, (2003 Oct) 2 (10) 1011-21. Journal code: 101132535. ISSN: 1535-7163.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20031028
Last Updated on STN: 20040603
Entered Medline: 20040602

AB SU11248 is an oral multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenic activities through targeting platelet-derived growth factor receptor, vascular endothelial growth factor receptor, KIT, and FLT3, the first three of which are expressed in human breast cancer and/or its supporting tissues. The purpose of the present studies was to demonstrate the potent anticancer activity of SU11248 alone or in combination with conventional cytotoxic agents against several distinct preclinical models of breast cancer. SU11248 was administered as a monotherapy to (1) mouse mammary tumor virus-v-Ha-ras mice and 7,12-dimethylbenz(a)anthracene-treated rats bearing mammary tumors and (2) mice bearing human breast cancer xenografts of s.c. MX-1 tumors and osseous metastasis of a MDA-MB-435-derived cell line (435/HAL-Luc). SU11248 was also administered in combination with docetaxel both in xenograft models and in combination with 5-fluorouracil and doxorubicin in the MX-1 model. SU11248 treatment potently regressed growth of mammary cancers in mouse mammary tumor virus-v-Ha-ras transgenic mice (82% regression) and 7,12-dimethylbenz(a)anthracene-induced mammary tumors in rats (99% regression at the highest dose; $P < 0.05$ for both). This agent also inhibited MX-1 tumor growth by 52%, with markedly enhanced anticancer effects when administered in combination with docetaxel, 5-fluorouracil, or doxorubicin compared with either agent alone ($P < 0.05$). SU11248 treatment in combination with docetaxel effectively prolonged survival of mice, with 435/HAL-Luc cancer xenografts established in bone compared with either agent alone ($P < 0.05$). These results demonstrate that SU11248 is effective in preclinical breast cancer models and suggest that it may be useful in the treatment of breast cancer in the clinic.

L47 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004015685 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14713109
TITLE: SU11248 inhibits tumor growth and CSF-1R-dependent osteolysis in an experimental breast cancer bone metastasis model.
AUTHOR: **Murray Lesley J**; **Abrams Tinya J**; Long Kelly R; Ngai Theresa J; Olson Lisa M; Hong Weiru; Keast

Paul K; Brassard Jacqueline A; O'Farrell Anne Marie; Cherrington Julie M; **Pryer Nancy K**
CORPORATE SOURCE: SUGEN, Inc. South San Francisco, California, USA.. drlesleymurray@yahoo.com
SOURCE: Clinical & experimental metastasis, (2003) 20 (8) 757-66. Journal code: 8409970. ISSN: 0262-0898.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20040110
Last Updated on STN: 20040123
Entered Medline: 20040122

AB The aim of the study was to investigate inhibitory effects of the receptor tyrosine kinase (RTK) inhibitor SU11248 against CSF-1R and osteoclast (OC) formation. We developed an in vivo model of breast cancer metastasis to evaluate efficacy of SU11248 against tumor growth and tumor-induced osteolysis in bone. The in vitro effects of SU11248 on CSF-1R phosphorylation, OC formation and function were evaluated. Effects on 435/HAL-Luc tumor growth in bone were monitored by in vivo bioluminescence imaging (BLI), and inhibition of osteolysis was evaluated by measurement of serum pyridinoline (PYD) concentration and histology. Phosphorylation of the receptor for M-CSF (CSF-1R) expressed by NIH3T3 cells was inhibited by SU11248 with an IC50 of 50-100 nM, consistent with CSF-1R belonging to the class III split kinase domain RTK family. The early M-CSF-dependent phase of in vitro murine OC development and function were inhibited by SU11248 at 10-100 nM. In vivo inhibition of osteolysis was confirmed by significant lowering of serum PYD levels following SU11248 treatment of tumor-bearing mice ($P = 0.047$). Using BLI, SU11248 treatment at 40 mg/kg/day for 21 days showed 64% inhibition of tumor growth in bone ($P = 0.006$), and at 80 mg/kg/day showed 89% inhibition ($P = 0.001$). Collectively, these data suggest that SU11248 may be an effective and tolerated therapy to inhibit growth of breast cancer bone metastases, with the additional advantage of inhibiting tumor-associated osteolysis.

L47 ANSWER 4 OF 6 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:501911 BIOSIS
DOCUMENT NUMBER: PREV200300498309
TITLE: Preclinical evaluation of the tyrosine kinase inhibitor SU11248 in combination with 'standard of care' therapeutic agents for breast cancer.
AUTHOR(S): **Murray, Lesley J.** [Reprint Author]; **Abrams, Tinya J.**; **Pryer, Nancy K.**; Walker, Vicky L.; Long, Kelly R.; Olson, Lisa M.; Pesenti, Enrico A.; Cherrington, Julie M.
CORPORATE SOURCE: SUGEN, Inc., S. San Francisco, CA, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 751-752. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Oct 2003
Last Updated on STN: 29 Oct 2003

L47 ANSWER 5 OF 6 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2003226905 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12748309
TITLE: SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer.
AUTHOR: **Abrams Tinya J**; Lee Leslie B; **Murray Lesley J**; **Pryer Nancy K**; Cherrington Julie M
CORPORATE SOURCE: Preclinical Research and Exploratory Development, SUGEN, Inc., South San Francisco, California 94080, USA.. tinya-abrams@sugen.com
SOURCE: Molecular cancer therapeutics, (2003 May) 2 (5) 471-8. Journal code: 101132535. ISSN: 1535-7163.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20030516
Last Updated on STN: 20040124
Entered Medline: 20040123

AB The purpose of this study was to evaluate the activity of the indolinone kinase inhibitor SU11248 against the receptor tyrosine kinase KIT in vitro and in vivo, examine the role of KIT in small cell lung cancer (SCLC), and anticipate clinical utility of SU11248 in SCLC. SU11248 is an oral, multitargeted tyrosine kinase inhibitor with direct antitumor and antiangiogenic activity through targeting platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor, KIT, and FLT3 receptors. Treatment of the KIT-expressing SCLC-derived NCI-H526 cell line in vitro with SU11248 resulted in dose-dependent inhibition of stem cell factor-stimulated KIT phosphotyrosine levels and proliferation. The biological significance of KIT inhibition was evaluated in vivo by treating mice bearing s.c. NCI-H526 tumors with SU11248 or another structurally unrelated KIT inhibitor, STI571 (Gleevec), which is also known to inhibit Bcr-Abl and PDGFRbeta. SU11248 treatment resulted in significant tumor growth inhibition, whereas inhibition from STI571 treatment was less dramatic. Both compounds reduced phospho-KIT levels in NCI-H526 tumors, with a greater reduction by SU11248, correlating with efficacy. Likewise, phospho-PDGFRbeta levels contributed by tumor stroma and with known involvement in angiogenesis were strongly inhibited by SU11248 and less so by STI571. Because platinum-based chemotherapy is part of the standard of care for SCLC, SU11248 was combined with cisplatin, and significant tumor growth delay was measured compared with either agent alone. These results expand the profile of SU11248 as a KIT signaling inhibitor and suggest that SU11248 may have clinical potential in the treatment of SCLC via direct antitumor activity mediated via KIT as well as tumor angiogenesis via vascular endothelial growth factor receptor FLK1/KDR and PDGFRbeta.

L47 ANSWER 6 OF 6 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:336896 BIOSIS
DOCUMENT NUMBER: PREV200300336896
TITLE: Characterization of SU11248 as a Potent Inhibitor of Flt3 in Preclinical Models.
AUTHOR(S): **Abrams, Tinya A.** [Reprint Author]; Ofarrell, Anne-Marie [Reprint Author]; Ngai, Theresa G. [Reprint Author]; Louie, Sharianne G. [Reprint Author]; Yuen, Helene A. [Reprint Author]; **Pryer, Nancy K.** [Reprint Author]; Manning, William C. [Reprint Author]; **Murray, Lesley J.** [Reprint Author]; Cherrington, Julie M. [Reprint Author]

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

CORPORATE SOURCE: Preclinical Research and Exploratory Development, SUGEN Inc, San Francisco, CA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 2199. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jul 2003
Last Updated on STN: 23 Jul 2003

AB The Flt3 receptor tyrosine kinase is a candidate for targeted molecular therapy in AML. Activating internal tandem duplication (ITD) mutations in the Flt3 juxtamembrane domain have been identified in blasts from 25-30% of AML patients, and are an independent negative prognostic factor for survival. SU11248 is a recently described small molecule inhibitor with specificity for split-kinase RTKs, including VEGFR2 (Flk-1/ KDR), PDGFR and c-kit. We show that SU11248 also has potent activity against wild type FLT3 (FLT3-WT) and FLT3-ITD. Accordingly, SU11248 inhibited FLT3-driven phosphorylation and induced apoptosis in MV4;11 (Flt3-ITD) and OC1-AML5 (Flt3-WT) leukemia cell lines. In addition, we report the novel finding that Flt3 signaling induces VEGF production, an inducer of angiogenesis, which is inhibited by SU11248 at nanomolar concentrations in vitro. In vivo SU11248 regressed FLT3-ITD tumors in a subcutaneous (SC) tumor xenograft model in a dose-dependent manner, with full regression at 20 mg/kg/day. Pharmacokinetic and pharmacodynamic (PK/PD) analysis showed that a single 20 mg/kg dose potently inhibits FLT3-ITD phosphorylation for up to 16 hours, and a plasma concentration of apprx30 ng/ml correlates with robust inhibition. To investigate activity in a leukemia-like disease, a bone marrow engraftment model was developed in cyclophosphamide treated mice, where inoculation of MV4;11 cells results in hind limb paralysis within 40-50 days. Daily administration of SU11248 prolonged paralysis-free survival in a dose-dependent manner, with full efficacy at 20 mg/kg. This correlated with decreased numbers of human cells in bone marrow by IHC and FACS analysis and decreased levels of human VEGF in plasma. These results predict that SU11248, which targets both angiogenesis and Flt3-driven proliferation is a promising candidate for FLT3-targeted therapy. SU11248 is currently in AML clinical trials.

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L50     1230869 FILE EMBASE
L51      667955 FILE CAPLUS

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L53           0 FILE MEDLINE
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L56          70 FILE CAPLUS

TOTAL FOR ALL FILES
L57         346 L9 AND L52
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Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

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L60           1 FILE EMBASE
L61           8 FILE CAPLUS

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L65           0 FILE EMBASE
L66           4 FILE CAPLUS

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L68  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:878170  CAPLUS
DOCUMENT NUMBER:          141:366237
TITLE:                    Preparation of indolinone compounds for treatment of
                          excessive osteolysis
INVENTOR(S):              Murray, Lesley; O'Farrell, Anne-Marie;
                          Abrams, Tinya
PATENT ASSIGNEE(S):       Sugen, Inc., USA
SOURCE:                   U.S. Pat. Appl. Publ., 34 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     US 2004209937         A1    20041021    US 2004-780917          20040219
     CA 2516786            AA    20040910    CA 2004-2516786         20040223
     WO 2004075775         A2    20040910    WO 2004-US405283        20040223
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             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
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             TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86
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WO 2004075775 A2 20040910 WO 2004-US5283 20040223
WO 2004075775 A3 20050414
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EP 1599207 A2 20051130 EP 2004-713729 20040223
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PRIORITY APPLN. INFO.: US 2003-448861P P 20030224
US 2004-780917 A 20040219
WO 2004-US5283 W 20040223
OTHER SOURCE(S): MARPAT 141:366237
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Disclosed is a method for treating excessive osteolysis in a patient, comprising administering to said patient an effective amount of a compound of formula (I) [wherein R = H, OH, alkyl, aryl, cycloalkyl, heteroaryl, alkoxy, heterocyclyl, amino; R1 = alkyl, halo, aryl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, heteroaryl, heterocyclyl, HO, COR8, NR9R10, NR9COR12, CONR9R10; R2 = alkyl, aryl, heteroaryl, COR8, SO2R''; (wherein R" = alkyl, aryl, heteroaryl, NR9R10, alkoxy); R5 = H, alkyl, aryl, haloalkyl, cycloalkyl, heteroaryl, heterocyclyl, HO, COR8, (CHR)rR11; X = O, S; p, r = 0-3; q = 0-2; wherein R8 = OH, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl, heterocyclyl; R9, R10 = H, alkyl, aryl, aminoalkyl, heteroaryl, cycloalkyl, heterocyclyl; or NR9R10 together forms a ring consisting of the ring atoms selected from the group consisting of C, N, O, and S; R11 = OH, NH2, mono- or disubstituted amino, alkyl, aryl, heteroaryl, alkoxy, cycloalkyl, heterocyclyl; R12 = alkyl, aryl, heteroaryl, alkoxy, cycloalkyl, heterocyclyl; Z = OH, O-alkyl, NR3R4; wherein R3, R4 = H, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl; or NR3R4 forms a ring consisting of the ring atoms selected from the group consisting of CH2, N, O, and S, or Q1; wherein Y = CH2, O, N, S; Q = C, N; n = 0-4; m = 0-3] or salts thereof. These compds. are useful for treating excessive osteolysis, by inhibiting M-CSF mediated osteoclast development. They are useful for inhibiting phosphorylation of colony-stimulating factor-1 receptor (CSF1R), and for treating **cancers** that express CSF1R. Thus, in a study on bone metastasis of **cancer**, 5-(5-Fluoro-2-oxo-1,2-dihydroindol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide (II) at 80 or 40 mg/kg per day for 21 days inhibited the growth of 435/HAL-luc breast **cancer** cells in bone by 89% in mice in 41 days after inoculation with **cancer** cells. Formulations, e.g. hard gelatin capsule containing II, were described.

IT **356068-94-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of indolinone compds. for treatment of excessive osteolysis, inhibiting phosphorylation of colony-stimulating factor-1 receptor (CSF1R), and treating **cancers** that express CSF1R)

RN 356068-94-5 CAPLUS
CN 1H-Pyrrole-3-carboxamide, 5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-N-[2-(1-pyrrolidinyl)ethyl]- (9CI) (CA INDEX NAME)

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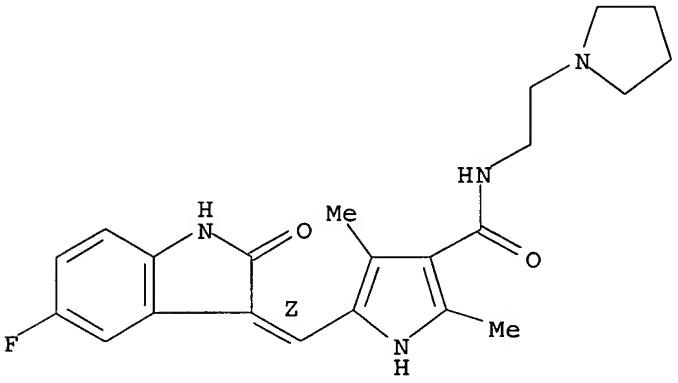


L68 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:943094 CAPLUS
DOCUMENT NUMBER: 141:33400
TITLE: Proof of target for SU11654: inhibition of KIT phosphorylation in canine mast cell **tumors**
AUTHOR(S): **Pryer, Nancy K.**; Lee, Leslie B.; Zadovaskaya, Regina; Yu, Xiaoming; Sukbuntherng, Juthamas; Cherrington, Julie M.; London, Cheryl A.
CORPORATE SOURCE: SUGEN,Inc, South San Francisco, CA, USA
SOURCE: Clinical Cancer Research (2003), 9(15), 5729-5734
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to evaluate the effect of the receptor tyrosine kinase inhibitor SU11654 on the activity of its mol. target KIT in canine mast cell **tumors** (MCT) and correlate target inhibition with mutational status of the c-kit juxtamembrane domain and SU11654 plasma concentration **Tumor** biopsies were obtained from dogs with advanced MCTs before and 8 h after administration of a single oral dose of SU11654, previously shown to be active in dogs with MCTs. Blood samples were taken to determine the plasma concentration of SU11654. Levels of phosphorylated KIT and ERK1/2 were assessed in **tumor** biopsies by Western blot. **Tumors** were analyzed by PCR for the presence or absence of an internal tandem duplication (ITD) in the juxtamembrane domain of c-kit. Fourteen dogs with advanced MCTs were enrolled in the study; 11 of these were evaluable for KIT target modulation (the remaining **tumor** specimens had inevaluable amts. of total KIT protein). Of these, eight MCTs showed reduced levels of phosphorylated KIT relative to total KIT after treatment with SU11654, compared with pretreatment biopsies. All four evaluable MCTs expressing ITD mutant c-kit showed modulation of KIT phosphorylation, as did four of seven **tumors** expressing non-ITD c-kit. Phosphorylated ERK1/2 was modulated in seven **tumors**; this did not correlate with inhibition of KIT phosphorylation. SU11654 treatment at the efficacious dose results in inhibition of KIT

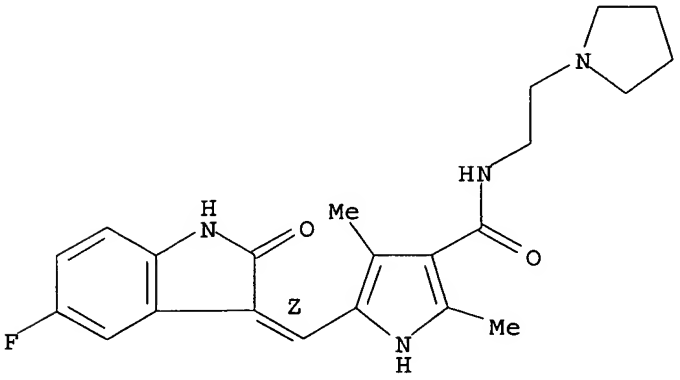
phosphorylation in canine MCTs.

IT **356068-94-5**, SU11654
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SU11654 effect on activity of mol. target KIT in canine mast cell **tumors**)

RN 356068-94-5 CAPLUS

CN 1H-Pyrrole-3-carboxamide, 5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-N-[2-(1-pyrrolidinyl)ethyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L68 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
DUPLICATE 1

ACCESSION NUMBER: 2003:240228 BIOSIS
DOCUMENT NUMBER: PREV200300240228
TITLE: SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo.
AUTHOR(S): O'Farrell, Anne-Marie [Reprint Author]; **Abrams, Tinya J.**; Yuen, Helene A.; Ngai, Theresa J.; Louie, Sharianne G.; Yee, Kevin W. H.; Wong, Lily M.; Hong, Weiru; Lee, Leslie B.; Town, Ajia; Smolich, Beverly D.; Manning, William C.; **Murray, Lesley J.**; Heinrich, Michael C.; Cherrington, Julie M.
CORPORATE SOURCE: SUGEN, 230 E Grand Ave, South San Francisco, CA, 94080, USA
marie-ofarrell@sugen.com
SOURCE: Blood, (May1 2003) Vol. 101, No. 9, pp. 3597-3605. print.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 21 May 2003
Last Updated on STN: 21 May 2003

AB FLT3 (fms-related tyrosine kinase/Flk2/Stk-2) is a receptor tyrosine kinase (RTK) primarily expressed on hematopoietic cells. In blasts from acute myelogenous leukemia (AML) patients, 2 classes of FLT3 activating mutations have been identified: internal tandem duplication (ITD) mutations in the juxtamembrane domain (25%-30% of patients) and point mutations in the kinase domain activation loop (7%-8% of patients). FLT3-ITD mutations are the most common molecular defect identified in AML

and have been shown to be an independent prognostic factor for decreased survival. FLT3-ITD is therefore an attractive molecular target for therapy. SU11248 is a recently described selective inhibitor With selectivity for split kinase domain RTKs, including platelet-derived growth factor receptors, vascular endothelial growth factor receptors, and KIT. We show that SU11248 also has potent activity against wild-type FLT3 (FLT3-WT), FLT3-ITD, and FLT3 activation loop (FLT3-Asp835) mutants in phosphorylation assays. SU11248 inhibits FLT3-driven phosphorylation and induces apoptosis in vitro. In addition, SU11248 inhibits FLT3-induced VEGF production. The in vivo efficacy of SU11248 was investigated in 2 FLT3-ITD models: a subcutaneous **tumor** xenograft model and a bone marrow engraftment model. We show that SU11248 (20 mg/kg/d) dramatically regresses FLT3-ITD **tumors** in the subcutaneous **tumor** xenograft model and prolongs survival in the bone marrow engraftment model. Pharmacokinetic and pharmacodynamic analysis in subcutaneous **tumors** showed that a single administration of an efficacious drug dose potently inhibits FLT3-ITD phosphorylation for up to 16 hours following a single dose. These results suggest that further exploration of SU11248 activity in AML patients is warranted.

L68 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:72786 CAPLUS
DOCUMENT NUMBER: 139:239801
TITLE: In Vivo Antitumor Activity of SU11248, a Novel Tyrosine Kinase Inhibitor Targeting Vascular Endothelial Growth Factor and Platelet-derived Growth Factor Receptors: Determination of a Pharmacokinetic/Pharmacodynamic Relationship
AUTHOR(S): Mendel, Dirk B.; Laird, A. Douglas; Xin, Xiaohua; Louie, Sharianne G.; Christensen, James G.; Li, Guangmin; Schreck, Randall E.; **Abrams, Tinya J.**; Ngai, Theresa J.; Lee, Leslie B.; **Murray, Lesley J.**; Carver, Jeremy; Chan, Emily; Moss, Katherine G.; Haznedar, Joshua O.; Sukbuntherng, Juthamas; Blake, Robert A.; Sun, Li; Tang, Cho; Miller, Todd; Shirazian, Sheri; McMahon, Gerald; Cherrington, Julie M.
CORPORATE SOURCE: Preclinical Research and Exploratory Development, SUGEN, Inc., South San Francisco, CA, 94080, USA
SOURCE: Clinical Cancer Research (2003), 9(1), 327-337
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB One challenging aspect in the clin. development of molecularly targeted therapies, which represent a new and promising approach to treating **cancers**, has been the identification of a biol. active dose rather than a maximum tolerated dose. The goal of the present study was to identify a pharmacokinetic/pharmacodynamic relationship in preclin. models that could be used to help guide selection of a clin. dose. SU11248, a novel small mol. receptor tyrosine kinase inhibitor with direct antitumor as well as antiangiogenic activity via targeting the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), KIT, and FLT3 receptor tyrosine kinases, was used as the pharmacol. agent in these studies. In mouse xenograft models, SU11248 exhibited broad and potent antitumor activity causing regression, growth arrest, or substantially reduced growth of various established xenografts derived from human or rat **tumor** cell lines. To predict the target SU11248 exposure required to achieve antitumor activity in mouse xenograft models, we directly measured target phosphorylation in **tumor** xenografts before and

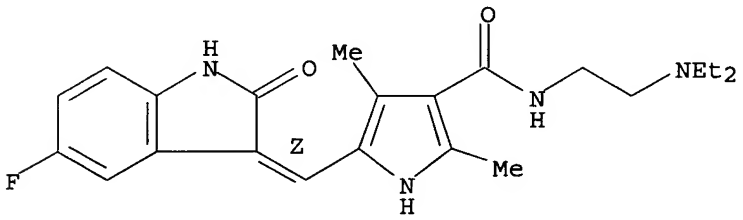
after SU11248 treatment and correlated this with plasma inhibitor levels. In target modulation studies in vivo, SU11248 selectively inhibited Flk-1/KDR (VEGF receptor 2) and PDGF receptor β phosphorylation (in a time- and dose-dependent manner) when plasma concns. of inhibitor reached or exceeded 50-100 ng/mL. Similar results were obtained in a functional assay of VEGF-induced vascular permeability in vivo. Constant inhibition of VEGFR2 and PDGF receptor β phosphorylation was not required for efficacy; at highly efficacious doses, inhibition was sustained for 12 h of a 24-h dosing interval. The pharmacokinetic/pharmacodynamic relationship established for SU11248 in these preclin. studies has aided in the design, selection, and evaluation of dosing regimens being tested in human trials.

IT **557795-19-4**, SU11248
RL: DMA (Drug mechanism of action); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship)

RN 557795-19-4 CAPLUS

CN 1H-Pyrrole-3-carboxamide, N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L68 ANSWER 5 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:79760 BIOSIS
DOCUMENT NUMBER: PREV200400075434
TITLE: The search for surrogates: Physiologic imaging in a breast **cancer** xenograft model during treatment with SU11248.
AUTHOR(S): Miller, K. D. [Reprint Author]; Miller, M.; Mehrotra, S.; Hutchins, G.; Badve, S.; **Murray, L. J.**; Sledge, G. W.
CORPORATE SOURCE: Indiana University, Indianapolis, IN, USA
SOURCE: Breast Cancer Research and Treatment, (2003) Vol. 82, No. Supplement 1, pp. S18. print.
Meeting Info.: 26th Annual San Antonio Breast Cancer Symposium. San Antonio, TX, USA. December 03-06, 2003.
ISSN: 0167-6806 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Feb 2004
Last Updated on STN: 4 Feb 2004

Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

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FILE 'REGISTRY' ENTERED AT 15:17:24 ON 09 DEC 2005
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L3 STR L1
L4 642 S L3 FUL

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L8 94 FILE CAPLUS
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L23 61 FILE EMBASE
L24 13 FILE CAPLUS
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L26 73 DUP REM L25 (3 DUPLICATES REMOVED)
L27 56 FILE MEDLINE
L28 111 FILE BIOSIS
L29 50 FILE EMBASE
L30 44 FILE CAPLUS
TOTAL FOR ALL FILES
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L32 695 FILE MEDLINE
L33 848 FILE BIOSIS
L34 560 FILE EMBASE
L35 376 FILE CAPLUS
TOTAL FOR ALL FILES
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L37 16 FILE MEDLINE
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L40 18 FILE CAPLUS
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L41 77 S PRYER N?/AU OR DRYER N?/AU

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L45            4 FILE CAPLUS
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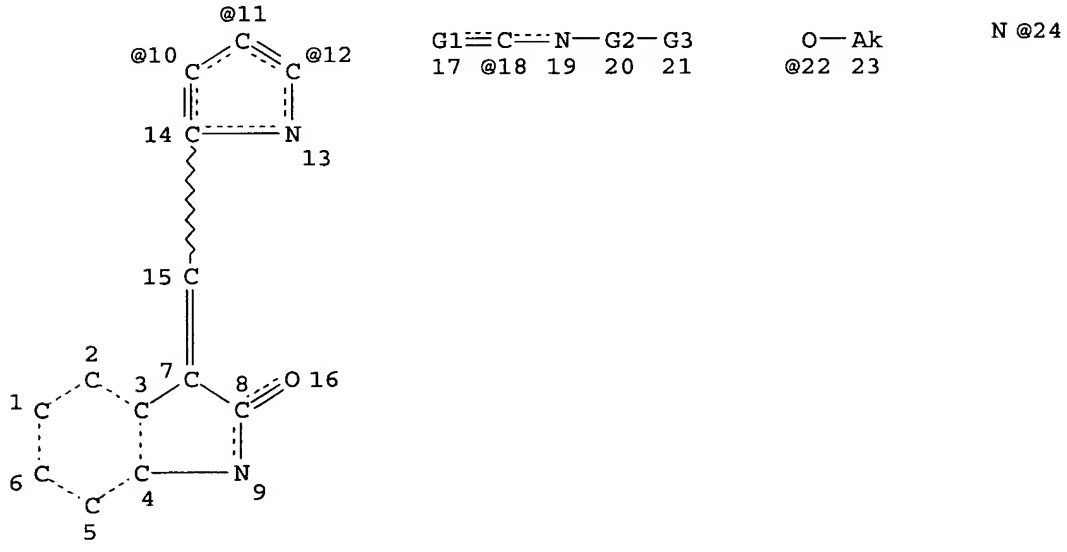


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Prepared by: Mary Hale @2-2507 Rem Bldg 1D86
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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
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